Colin Gonsalves
Senior Advocate

4664

LISTED ON. 2/7/19
COURT NO. 1
ITEM NO. 13

D.NO. 15142/19

IN THE SUPREME COURT OF INDIA

Civil Original Jurisdiction

Writ Petition (Civil) 689 of 2019

[Under Article 32 of the Constitution of India]

In The Matter of:

Amit Kumar Agarwal & Ors. ... Petitioners

Versus

Union of India & Ors. ... Respondents

PAPER BOOK

INDEX

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I.A. NO. 82581 of 2019 : Application seeking permission to file lengthy synopsis and List of dates.

Filed on. 24/4/19

Advocate for Petitioner_Satya Mitra

ITEM NO.13 COURT NO.1 SECTION X

S U P R E M E C O U R T O F I N D I A
RECORD OF PROCEEDINGS

Writ Petition (Civil) No. 689/2019

AMIT KUMAR AGARWAL & ORS. Petitioners

VERSUS

UNION OF INDIA & ORS. Respondents

(FOR ADMISSION and IA No.82581/2019-PERMISSION TO FILE SYNOPSIS AND LIST OF DATES)

Date : 02-07-2019 This matter was called on for hearing today.

CORAM :
HON'BLE THE CHIEF JUSTICE
HON'BLE MR. JUSTICE DEEPAK GUPTA
HON'BLE MR. JUSTICE ANIRUDDHA BOSE

For Petitioners
Mr. Colin Gonsalves, Sr. Adv.
Ms. Sneha Mukherjee, Adv.
Mr. Satya Mitra, AOR

For Respondents

UPON hearing the counsel the Court made the following
O R D E R

At this stage, the Court is inclined to issue limited notice to the Medical Council of India to take on record its views as to whether the stem cell transplant procedure adopted could have been so done in accordance with the norms in force.

(Deepak Guglani)
Court Master

(Anand Prakash)
Court Master

Index of Record of Proceedings

Sn.	Date of Records of Proceedings	Pages
1.	Court's order dated.....	
2.	Court's order dated.....	
3.	Court's order dated.....	
4.	Court's order dated.....	
5.	Court's order dated.....	
6.	Court's order dated.....	
7.	Court's order dated.....	
8.	Court's order dated.....	
9.	Court's order dated.....	
10.	Court's order dated.....	
11.	Court's order dated.....	
12.	Court's order dated.....	
13.	Court's order dated.....	
14.	Court's order dated.....	

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1.	Listing Proforma	A1-A2	A1-A2	
2.	Cover Page of Paper Book		A3	
3.	Index of Record of Proceeding		A-4	
4.	Defect List/WRIT PROFORMA		A-5	
5.	Note Sheet		NS1+	
6.	Synopsis and List of Dates	B-55		
7.	Writ Petition with Affidavit	1-57		
8.	Appendix A true copy of the relevant provisions of the Drugs and Cosmetics Act, 1940.	58-63		
9.	Annexure P-1 A true typed copy of "Haploidentical Bone Marrow Transplant" published by the John Hopkin Medicine, Sidney Kimmel Cancer Centre, dated- Nil.	64-67		

10.	Annexure P-2 A true copy of the prescription of Manipal Hospital signed by Dr. Satyendra Katewa, explaining the procedure, dated- Nil.	68		
11.	Annexure P-3 A true copy of the recording of conversation between Petitioner No. 3 and Respondent No. 4, dated – Nil.	69		
12.	Annexure P-4 A true typed copy of the transcript of telephonic conversation between Petitioner No. 2 and Respondent No. 4.	70-82		
13.	Annexure P-5 A true typed copy of "Allogenic stem cell transplantation for thalassemia major in India" published by Department of Haematology, Christian Medical College, Vellore, India dated 09.02.2018.	83-84		
14.	Annexure P-6 A true typed copy of RTI response by the Indian Council of Medical Research dated 25.07.2018.	85-87		

15.	Annexure P-7 A true typed copy of extract of website of Fortis Hospital Memorial Research Institute, Gurugram, dated – Nil.	88-89		
16.	Annexure P-8 A true copy of the transcript of the video of Fortis Hospital Memorial Research Institute, Gurugram, dated- Nil.	90		
17.	Annexure P-9 A true typed copy of "Your support could save baby Radhika from lifelong blood transfusion" published by MILAAP, dated- Nil.	91-93		
18.	Annexure P-10 A true typed copy of the RTI replies by Government of India, dated – 11.03.2018.	94		
19.	Annexure P-11 A true typed copy of RTI reply of the Government of Rajasthan, dated-14.05.2018.	95-97		
20.	Annexure P-12 A true typed copy of the RTI response by Soni Manipal Hospital dated 28.04.2018.	98-100		

21.	Annexure P-13 %. A true typed copy of "Alternative donor transplant of benign primary hematologic disorders" written by J. Tolar , P. Sodani and H. Symons and published by Macmillan Publishers Limited, 2015, dated- Nil.	101-118		
22.	Annexure P-14 A true typed copy of the relevant extract of the "Minimum Standards for Haematopoitic Stem Cell Transplantation (HSCT) Units for Blood Diseases, dated- Nil.	119-121		
23.	Annexure P-15 A true typed copy of the relevant portion of the " National Guidelines for Stem Cell Research, 2013" , dated- Nil.	122-190		

24.	Annexure P-16 A true typed copy of the Letter by Ms. Maneka Sanjay Gandhi, Hon'ble Minister, Women and Child Development addressed to Shri. Jagat Prakash Nadda, Hon'ble Minister of Health and Family Welfare, dated- 02.05.2018.	191		
25.	Annexure P-17 A true typed copy of the detailed estimates of expenses of the petitioners including the date of death and the expenses incurred dated – Nil.	192-194		
26.	Annexure P-18 A true typed copy of F.I.R No. 0325 of 2018 registered at Vidhyadhar Nagar, dated-28.06.2018.	195-204		
27.	Annexure P-19 A true typed copy of F.I.R No. 0326 of 2018 registered at Vidhyadhar Nagar, dated-29.06.2018.	205-216		

28.	Annexure P-20 A true typed copy of F.I.R No. 0456 of 2018 registered at Vidhyadhar Nagar, dated-25.09.2018.	217-230		
29.	Annexure P-21 A true typed copy of the Final Report No. 109/2018 in F.I.R no. 0137 of 2018 dated 15.07.2018.	231-234		
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A1

PROFORMA FOR FIRST LISTING

SECTION_____

The case pertains to (Please tick/check the correct box):

☐ Central Act: (Title) The Drugs and Cosmetics Act, 1940

☐ Section: Schedule Y of the Act and Appendix V

☐ Central rule: (Title) N.A.

☐ Rule No(s): N.A.

☐ State Act (Title) N.A.

☐ Section: N.A.

☐ State Rule (Title) N.A

☐ Rule No(s): N.A

Impugned Interim Order Date: N.A.

☐ Impugned Final Order/Decree Date: N.A.

☐ High Court Name: N.A.

☐ Name of Judges: N.A

☐ Tribunal/Authority (Name): N.A.

1. Nature of matter: ☑ Civil ☐ Criminal

(a) Petitioner/Appellant No.1: Amit Kumar Agarwal

2. (b) E-mail ID: ksp.patna@gmail.com

(c) Mobile Phone Number: 9431011493

3. (a) Respondent No.1: Union of India

(b) e-mail ID: NA

(c) Mobile Phone Number: NA

4. (a) Main category classification: 08 and ors

(b) Sub classification: 0807 and ors.

5. Not to be listed before: N.A.

6. (a) Similar disposed of matter with citation, if any, &

case details: No similar matter pending A2

(b) Similar pending matter with case details: N.A. Similar matter is pending

7. **Criminal Matters:** N.A.

a. Whether accused/convict has surrendered: Yes ☐ No ☐

b. FIR No. N.A. Date: N.A.

c. Police Station: N.A.

d. Sentence Awarded: N.A.

e. Period of sentence undergone including period of detention/custody undergone:

8. **Land Acquisition Matters:** N.A.

(a) Date of Section 4 notification: N.A.

(b) Date of Section 6 Notification: N.A.

(c) Date of Section 17 notification: N.A.

9. **Tax Matters:** State the tax effect: N.A.

10. **Special Category** (first petitioner/appellant only):

☐ Senior citizen > 65 years ☐ SC/ST ☐ Woman/Child

☐ Disabled ☐ Legal Aid case ☐ In custody

11. Vehicle Number (in case of Motor Accident Claim matters):

N.A.

12. Decided case with citation:

Date: 24/4/2019

Satya Mitra

(AOR for Petitioner)

Registration No. 1852

Email: satyamitra2003@gmail.com

SYNOPSIS

B

The main issue

1. The 10 petitioners are parents of 10 children aged 5 – 18 years who underwent Haploidentical Stem Cell Transplant and died from April 2015 to December 2016 in Manipal Hospital, Jaipur (R-3) as a result of Heplo Stem Cell Transplant (Heplo SCT) carried out by Dr. Satyender Katewa (R-4). They come from different states of India, i.e. Bihar, Uttar Pradesh, Haryana, Rajasthan, Delhi, West Bengal. This was offered as a therapy to the Petitioners, but in actual, this is still a clinical trial worldwide (at Annexure P- 5 at Page 83 to 84) carried out completely lawlessly, in all probability on behalf of a foreign corporation, and without any of the approvals required under The Drugs and Cosmetics Act, 1940. They were done without taking the informed consent of the petitioners. They were carried out with the knowledge and the understanding that the children would die in the process. When the first child died in 2015 the trials were not discontinued. Even after the children began dying one after the other the trial continued mercilessly without regard for human life.

2. Similar proceedings are reported to be going on in different hospitals in different states of India such as Delhi, Maharastra, Rajasthan, Karnataka, Uttar Pradesh, West Bengal etc. Petitioners, however, are not aware of the position regarding mortality of children and adults in these hospitals in the various states, however, according to the Drug

Controller, State of Rajasthan; the percentage of deaths (within 100 days) at Soni Manipal Hospital is comparable to the deaths recorded in other hospitals in India. The private hospitals in the various states carrying out Haplo SCT procedures unlawfully are, among others, Fortis Research Memorial Institute, Gurugram, Medanta Multi Super Speciality Hospital, Gurugram, B.L. Kapoor Super Speciality Hospital, Delhi, Dharamshila Cancer Hospital and Research Centre, Delhi, Prem Niketan Hospital, Jaipur, Ruby Hall Cancer Centre, Pune. In view of the unlawful trials being carried out in different states of India, petitioners have filed this writ petition under Article 32 of the Constitution of India for the following reliefs:

i) for an injunction stopping all Haplo Stem Cell Transplant therapy /trials for children with Thalassemia disorder in the country until efficacy is proven.

ii) for the prosecution of those involved in the clinical trials/therapy, misleading parents which lead to the death of several children.

Thalassemia

3. The trial is done on persons suffering from thalassemia major/inter media (hereinafter Thalasemia). Thalassemia is a disorder which arises when the red blood cells self destruct at a more than normal rate. The standard treatment worldwide is regular blood transfusion done on regular intervals with medication. This is not a life threatening situation provided regular blood transfusion is available, affordable and is done.

D

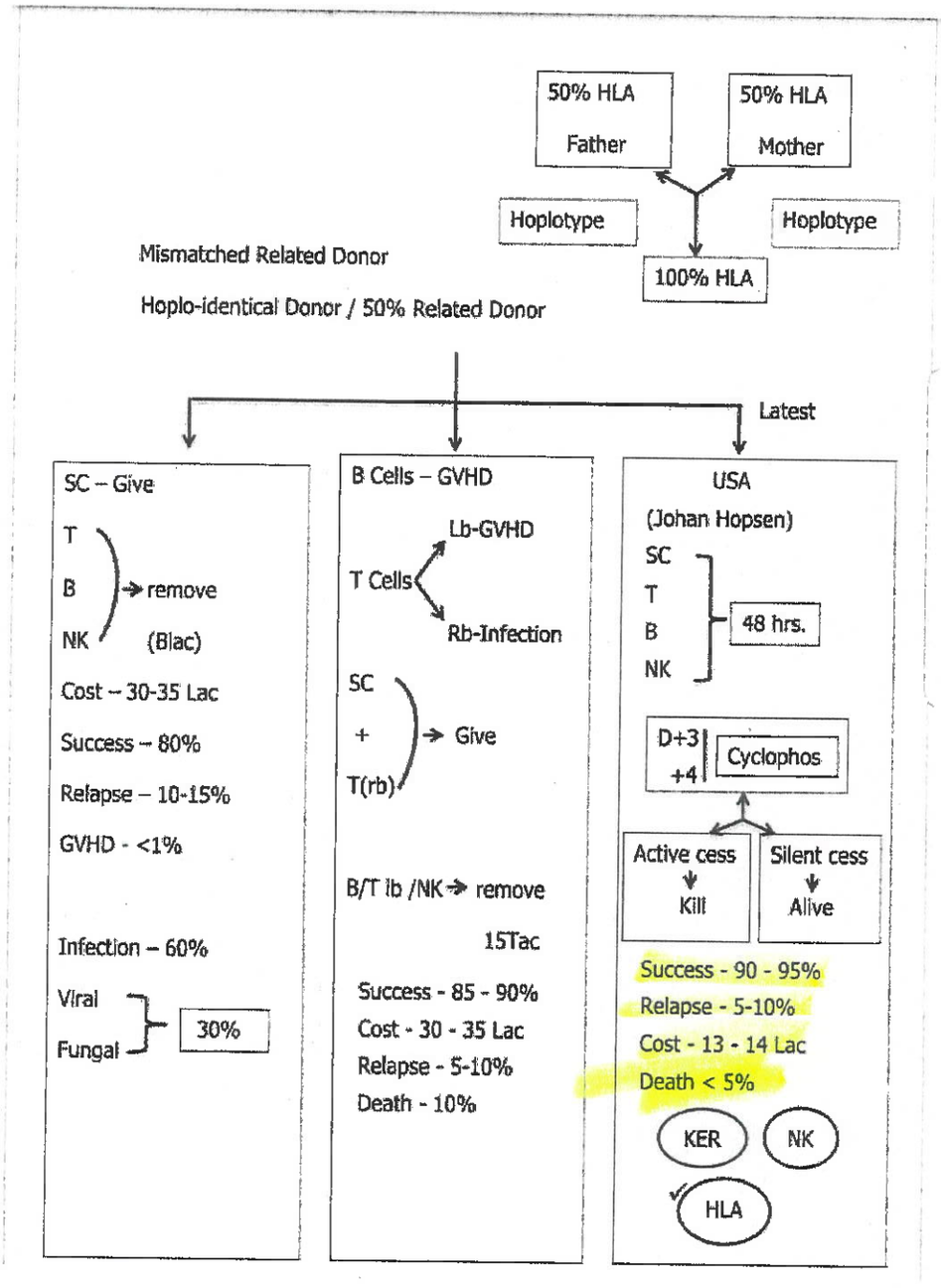
4. Thalassemia is not curable except in a situation where a 100% Human Leukocyte Antigen (HLA) good match is possible between the donor and the recipient. This is commonly known as stem cell transplant and in common parlance often referred to as bone marrow transplant. Such transplants with a 100% HLA match are well recognised procedure throughout the world as well as in India and the success rate is around 90% where it may be said that Thalassemia is cure. In most other cases there is no cure and the patient has to undergo a lifetime of blood transfusion which is the standard care with negligible life threat.

5. The Heplo SCT trial involves the infusion of stem cells with a less than 100% HLA match with the donor. Such procedures have not been approved by the authorities anywhere in the world as a therapy and are only done as a clinical trial. The question that arises in this petition is whether clinical trials as were done in the present instance were lawful at all.

Informed consent

6. Not only was informed consent not taken, on the contrary the petitioners were misled into believing that the success rate for the trials would be in excess of 90% and also without any risks. This was given by Dr. Satyernder Katewa (R-4) in writing (at Annexure P-2 page — to 68) and a sample is set out herein below:

E



7. Petitioners also have an audio recording of the said doctor, a transcript of which is at Annexure P-3 page — to 69 and the relevant part of which is as under:

"Petitioner- I have no complaints against you, Sir. I have only two requests. That you tell patients the correct success ratio and cost of the procedure.

F

Dr. Satyendra Katwa- Look Prem Ji, whoever comes to me I tell them- here are my new patients, there are my old patients. When I told you about the USA paper, at that time there was no available data concerning India. That was when we started. Nobody in India had tried out the procedure by that time. Now, I have data about the 30 patients on which I tried the procedure- now I can tell you what the data concerning India is. Now I tell the patients that the USA paper gives a particular success rate, but it is not applicable in India where the success rate is much lower."

8. The statutory regime for obtaining informed consent is set out in Schedule Y of the Act and Appendix V to the Schedule which is as under:

"(4) Informed Consent

(i) In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject. The Subject's consent must be obtained in writing using an 'Informed Consent Form'. Both the patient information sheet as well as the Informed Consent Form should have been approved by the ethics committee and furnished to the Licensing Authority.

Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

(ii) Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative (a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India). If the Subject or his/her legally acceptable representative is unable to read/write – an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(ii) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the Informed Consent Form for study Subjects is given in Appendix V.

Appendix V

H

INFORMED CONSENT

1. Checklist for study Subject's informed consent documents

1.1 Essential Elements:

1. Statement that the study involves research and explanation of the purpose of the research

2. Expected duration of the Subject's participation 535 Drugs and Cosmetics Rules, 1945

3. Description of the procedures to be followed, including all invasive procedures and

4. Description of any reasonably foreseeable risks or discomforts to the Subject

5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.

6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.

7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records.

I

8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)

9. Compensation and/or treatment(s) available to the Subject in the event of a trial related injury

10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury

11. The anticipated prorated payment, if any, to the Subject for participating in the trial

12. Subject's responsibilities on participation in the trial

13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled.

14. Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.

15. Statement that in the case of placebo controlled trial, the placebo administered to the subject shall not have any therapeutic effect.

J

16. Any other pertinent information.

1.2 Additional elements, which may be required:

(a) Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.

(b) Additional costs to the Subject that may result from participation in the study .

.(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.

(d) Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may . affect the Subject's willingness to continue participation will be provided.

(e). A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus, if the Subject is or may become pregnant), which are currently unforeseeable

(f) Approximate number of Subjects enrolled in the study

K

2. Format of informed consent form for Subjects participating in a clinical trial-----

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject Initials: Subject's name:

Date of Birth/Age:

[Address of the Subject

Qualification

Occupation: Student/Self-employed/Service/Housewife/Others (Please tick as appropriate)

Annual Income of the subject

Name and address of the nominee(s) and his relation to the subject (for the purpose of compensation in case of trial related death).]

Place initial

Box (subject)

(i) I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without 'giving any reason, without my medical care or legal rights being affected,

(iii)I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) Signature (or Representative: ------ Thumb impression) of the Subject/Legally Acceptable

(v) I agree to take part in the above study.

Date: _~/_~/ __

Signatory's Name:

M

_ Signature of the Investigator:

Date:

Study Investigator's name:

Signature of the witness

Date

Name of Witness:

[Copy of the patient information sheet and duly filled informed consent form shall be handed over to the subject or his/her attendant.]"

In the present case the patients were not informed of their rights before agreeing to undergo a clinical trial (in fact they had no idea that this was an experiment and were given the impression that this was a well established and approved treatment worldwide with negligible risk to the life of their children), and it was only after 60% of the procedure was over were they given a standard form on which they were told to sign. Copy of that form was not given to them and it remains with the doctor and the hospital. They were given the forms and told to sign in a cursory and mechanical fashion; the forms were taken back on the spot. The parents were not in a position to decline to sign as their children were undergoing the procedures and their immune system was suppressed by the administration of drugs and were the drugs to be discontinued, the children would have died.

9. Referring once again to the statutory regime set out above, petitioners state that informed consent was never taken and did not even attempted, the patients were not covered by medical insurance, they were never informed of the hazards of the clinical trial, they were not told of less hazardous treatments, the cost of treatment at the initial stages was indicated at Rs. 8 – 12 lakhs and the ultimate costs turned out to be Rs. 50 – 60 lakhs per child and some cases the expenses ran into crores of rupees.

The statutory regime for approvals

10. Schedule Y of the Drugs and Cosmetics Act, 1940 lays down the rules and regulations for conducting clinical trials in India. The rules are enumerated as below:

"2. Clinical Trial:

(1) *Approval for clinical trial*

(i) Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under rule 21 (b), and the approval obtained from the respective ethics committee (s). The Licensing Authority as defined shall be informed of the approval of the respective institutional ethics committee(s) as prescribed in Appendix VIII, and the trial initiated at each respective site only after obtaining such an approval for that site. The trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an independent ethics committee (constituted as per Appendix

VIII), provided that the approving ethics committee(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.

(ii) All trial Investigator(s) should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol. A qualified physician (or dentist, when appropriate) who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. Laboratories used for generating data for clinical trials should be compliant with Good Laboratory Practices. If services of a laboratory or a facilities outside the country are to be availed, its/their name(s), address(s) and specific services to be used should be stated in the protocol to avail Licensing Authority's permission to send clinical trial related samples to such laboratory(ies) and/or facility(ies). In all cases, information about laboratory(ies) / facilities to be used for the trial, if other than those at the investigation site(s), should be furnished to the Licensing Authority prior to initiation of trial at such site(s).

(iii) Protocol amendments if become necessary before initiation or during the course of a clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the ethics committee which has granted the approval for the study. No deviations from or changes to the protocol should be implemented without prior

written approval of the ethics committee and the Licensing Authority except when it is necessary to eliminate immediate hazards to the trial Subject(s) or when change(s) involve(s) only logistic or administrative aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Licensing Authority. Administrative and/or logistic changes in the protocol should be notified to the Licensing Authority within 30 days.

(2) *Responsibilities of Sponsor:-*

(i) The clinical trial Sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice (GCP) Guidelines issued by the Central Drugs Standard Control Organization, Directorate General of Health Services, Government of India as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with GCP and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical trial to the Licensing Authority at the prescribed periodicity.

(iii) In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug

reactions (Appendix XI), if any, and the reason for discontinuation of the study or non-pursuit of the new drug application.

[(iv) Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Licensing Authority as referred to in clause (b) of rule 21, the Chairman of the Ethics Committee and the head of the institution where the trial has been conducted, within fourteen days of the occurrence of the serious adverse event.]

(v) in case of injury or death occurring to the clinical trial subject, the Sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever, had obtained permission from the Licensing Authority for conduct of the clinical trial, shall make payment for medical management of the subject and also provide financial compensation for the clinical trial related injury or death in the manner as prescribed in Appendix XII;

(vi) the Sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, shall submit details of compensation provided or paid for clinical trial
related injury or death, to the Licensing Authority within thirty days of the receipt of the order of the Licensing Authority.]

[(3)(i)] *Responsibilities of the Investigator(s):*

The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII. Standard operating

procedures are required to be documented by the investigators for the tasks performed by them. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events. Investigator(s) shall report all serious and unexpected adverse events to the [3][Licensing Authority defined under clause (b) of rule 21, the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their

occurrence. [In case, the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event. The report of the serious adverse event, after due analysis, shall be forwarded by the Investigator to the Licensing Authority as referred to in clause (b) of rule 21, the Chairman of the Ethics Committee and the Head of the institution where the trial has been conducted within fourteen days of the occurrence of the serious adverse event.]].

[(ii) The Investigator shall provide information to the clinical trial subject through informed consent process as provided in Appendix V about the essential elements of the clinical trial and the subject's right to claim compensation in case of trial related injury or death. He shall also inform the subject or his/her nominees(s) of their rights to contact the Sponsor or his representative whosoever had obtained permission from the Licensing

Authority for conduct of the clinical trial for the purpose of making claims in the case of trial related injury or death.]

(4) *Informed Consent:-*

(i) In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject. The Subject's consent must be obtained in writing using an Informed Consent Form'. Both the patient information sheet as well as the Informed Consent Form should have been approved by the ethics committee and furnished to the Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

(ii) Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative (a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India). If the Subject or his/her legally acceptable representative is unable to read/write – an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(iii) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the Informed Consent Form for study Subjects is given in Appendix V.

[(iv) An audio-video recording of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and understanding on such consent, shall be maintained by the investigator for record:

Provided that in case of clinical trial of anti-HIV and anti-Leprosy drugs only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.]

(5) Responsibilities of the Ethics Committee:

(i) It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and well being of all trial subjects. The ethics committee should exercise particular care to protect the rights, safety and well being of all vulnerable subjects participating in the study, e.g., members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, umemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally giving consent. Ethics

committee(s) should get document standard operating procedures and should maintain a record of its proceedings.

(ii) Ethics Committee(s) should make, at appropriate intervals, an ongoing review of the trials for which they review the protocol(s). Such a review may be based on the periodic study progress reports furnished by the investigators and/or monitoring and internal audit reports furnished by the Sponsor and/or by visiting the study sites.

(iii) In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the Investigator as well as to the Licensing Authority.

[(iv) In case of serious adverse event occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as referred to in clause (b) of rule 21 for conducting the clinical trial, to the Licensing Authority within thirty days of the occurrence of the serious adverse event.

[5(A). *Serious Adverse Events:-*

(1) A serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalization (in case

the study was being conducted on outpatient), prolongation of hospitalization (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening.

(2) The Investigator shall report all serious 3 [***] adverse events to the Licensing Authority as defined under clause (b) of Rule 21, the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurrence as per Appendix XI and the said Licensing Authority shall determine the cause of injury or death as per the procedure prescribed under Appendix XII and pass orders as deemed necessary. [3][In case, the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event.

(6) *Human Pharmacology (Phase I):-*

(i) The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into human(s). Studies in this Phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients. Phase I trials should preferably be carried out by Investigators trained in clinical pharmacology

with access to the necessary facilities to closely observe and monitor the Subjects.

(ii) Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives:-

(a) *Maximum tolerated dose*: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.

(b) Pharmacokinetics, i.e., characterization of a drug's absorption, distribution, metabolism and excretion. Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

(c) *Pharmacodynamics*: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic/ pharmacodynamic studies) may be conducted in healthy volunteer Subjects or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

(d) Early Measurement of Drug Activity: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later Phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

(7) *Therapeutic exploratory trials (Phase II):-*

(i) The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this Phase is to determine the dose(s) and regimen for Phase III trials. Doses used in Phase II are usually

(but not always) less than the highest doses used in Phase I.

(ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

(iii) If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority.

(8) *Therapeutic confirmatory trials (Phase III):-*

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s). Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drug(s).

(ii) For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).

(iii) For new drugs approved outside India, Phase III studies need to be carried out primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

(iv) If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to the Licensing Authority along with the application.

(9) *Post Marketing Trials (Phase IV):-*

Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/morbidity studies, epidemiological studies etc."

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Bone marrow transplant and Haplo SCT

11. Bone marrow transplant for patients with Thalassemia is well recognised procedure throughout the world and in India. This is performed only when the donor and the recipient have a 100% match. The success rate is approximately 90%. It is an almost safe procedure. The Haplo SCT procedure is not approved anywhere in the world. This is performed when the recipient and the donor have a match that is less than 100%. In the present instances where deaths have occurred the match was 50% onwards but less than 100%. In such a situation no procedure should have been carried out on the children.

12. It is important to note that the children were stable and would continue to be stable for the rest of their lives. All that had to be done was to keep them on medication and regular blood transfusion once or twice a month. Thus, there was no emergency requiring any unapproved procedure or clinical or high risk procedure to be carried out on them. Nor was there any need to carry out a clinical trial on the children.

13. The Monitoring body in the country is the "Indian Stem Cell Transplant Registry" which operates under the Department of Haematology, Christian Medical College, Vellore. In a paper recently published in the Paediatric Haematology Oncology Journal in 2018 titled "Allogeneic stem cell transplantation for thalassemia major in India" (at Annexure P- 5 page 83 to 84), the conclusion was as under:

> "There is a lot of interest in haplo-identical stem cell transplantation in the world over the last few years.

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Novel conditioning and GVHD prophylxis regimens have resulted in dramatic improvements in clinical outcome even without T cell depletion of the graft. There is however very limited data in thalassemia major. In one small series (n=22) using T cell depletion grafts the graft rejection rate was 27% and the TFS about 67%. More recently the use of grafts with depletion of CD3aß T cells looks promising with a few successful reports (44). In a disease where several management options exist and newer ones are on the horizon, whether a treatment option that gives less than -80% TFS can or should be recommended needed further discussion. Haplo-identical SCT therefore cannot be recommended at this time outside the setting of a clinical trial."

14. It is submitted that the abovementioned Registry is the body which coordinates activities relating to stem cell transplants in India and is the leading authority on the subject. All parties intending to do research or any activity relating to such transplants are required by the central government to register with the "National Apex Committee for Stem Cells and Research". The respondent Hospital has not registered. Evidence of this is a reply dated 25.7.18 (at Annexure P - 6 page 85 to 87) received from the Indian Council of Medical Research (ICMR) in response to a query under RTI which is as under:

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"Question: Is Manipal Hospital (old name Soni Manipal Hospital) registered with your body, The National Apex Committee for Stem Cell Research and Therapy Department of Health Research, Govt. Of India?

Answer: No.

Question: Can any organization/institute or Hospital who is not registered with the National Apex Committee for Stem Cell Research and Therapy Department of Health Research, Govt. Of India perform Heplo Stem Cell Transplant and Heplo Bone Marrow Transplant?

Answer: It is mandatory to constitute and register Institutional Committee for Stem Cell Research (NAC SCRT) for any institute/hospital/entity/ institute in Stem Cell Research. The hospital cannot conduct clinical trials/therapy using stem cells for disease/conditions other than listed in Annexure III of National Guidelines."

15. The website of Fortis Hospital Memorial Research Institute, Gurgaon, has the following on the website (at Annexure P-7 page 88-89):

"40 percent long term outcome data for haploidentical transplant"

16. Similarly, the website of Milaap which does crowd funding for patients who need assistance have a story on their website at Annexure P-9 Pg. 91 to 93 and the relevant part is as under:

"We have been explained that Haploidentical BMT is currently not established as standard of care for Thalassemia Major, and same is carried out in institutionally approved clinical study"

17. In the case of a 100% match when the donor marrow is inserted in the recipient's body there is an automatic resistance to the foreign substance being injected by the body's immune system. This is overcome by chemotherapy which helps the grafting process by weakening the immune system. Where there is partial match the chemotherapy regime is very intense so as to breakdown the immune system completely. The efficacies of the medicines that are needed to counter act this breakdown have not yet been proved in the world. This is how the deaths took place.

18. In reply dated 11.3.18 at Annexure P-10 page – to 94 in response to an RTI application, Government of India stated as under:

"I am directed to refer to your RTI application dated 29.01.2018 requesting information under the RTI Act, 2005. In So far as NHM-1 section under Ministry of Health and Family Welfare is concerned. It is stated that no approval/recognition has been given by this division to the Heplo Stem Cell Transplant for Thalassemia affected children."

19. Similarly, in a reply dated 14.5.18 under RTI (at Annexure P- 11 page 95 to 97) government of Rajasthan stated as under:

"Question: Kindly inform us if your department has provided/given approval for Haplo Bone Marrow Transplant or Haplo Stem Cell Transplant.

Answer: The Directorate of Health and Family Welfare, Government of Rajasthan has not given approval for Heplo Bone Marrow Transplant and Heplo Stem Cell Transplant."

20. Several complaints were made to Additional Chief Secretary, Govt of Rajasthan, Medical and Health & other authorities against unethical clinical trial by Dr Satyendra Katewa and Manipal Hospital Jaipur, But no action was informed to the Petitioners till May 2018. But when question through RTI was raised to the above said department to provide details of complainants etc, Petitioners found in reply that Several letters were issued by Above said department, and was copy marked to the Petitioners, but copy was not sent to the petitioners,

21. The Directorate of Health wrote to the Registrar, Medical Council of Rajasthan to initiate investigation against Dr. Katewa & Manipal Hospital Jaipur. In the letters addressed to the Rajasthan Mecial Council, the Directorate of Health stated that an enquiry Committee was formed vide letter no. 642/2018 dated 04.04.2018 and letter no. 837/2018 dated 07.04.2018 , however they refused to conduct such enquiry on the ground that they did not have the power and authority to conduct such enquiry against a private hospital or doctor. The Committee further informed the Director, Department of Health and Family Welfare, Government of Rajasthan that the Rajasthan Medical Council was empowered to conduct such enquiry. I

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22. In a reply dated 28.4.18 at Annexure P-12 page 98 to 100 the Soni Manipal Hospital gave a reply under RTI filled to Govt. of Rajasthan (Dept. Of Health) illegally forwarded to Manipal Hospital, Jaipur instead of responding themself and Manipal Hospital sent bunch of papers to Petitioner with irrelevant non trustable sentences and is as under:

> "Question: Is Haplo indentical Bone Marrow Transplant (BMT) approved by the government?
>
> Answer: Haploidentical transplants are a sub-type of BMT and since in BMT there is no involvement of organs being taken out from donors, and again (putting) implanting in a patient, BMT doesn't come under "Transplant of Human Organ Act", (THOA) 1994. The above act to the best of our knowledge has been amended twice by the government of India in 2011 and 2014 and BMT doesn't come under the scope of this Act which means it doesn't need any approval from Government Agencies."

The abovementioned reply shows that the hospital/doctor has made a false statement to the effect that the petitioners have preceded with the trial after giving written consent whereas the petitioner has described the manner in which their signatures were taken on a form. The petitioners have also stated that such signatures were taken midway during the trial when they had no option but to continue or else their children would have died.

23. The reply of the hospital also states that this type of procedure did not require approval which actually was a clinical trial. The reply further

states, that the success rate of their Centre was 60% which proves that both the Hospital and the Doctor mislead the families of the patients with high success ratio of 90-95%. Relevant portion of the RTI reply is stated below:

> "We have done 26 Thalassemia Heplo Identical BMT at Manipal Hospital Jaipur over the last 2 ½ years. Out of 26 Haploidentical BMT, we lost 8 kids due to BMT complications in less than 100 days post BMT (TRM) which makes mortality rate around 30% and BMT success ratio around 70%. Since we have lost 3 more kids after 100 days of BMT(these three kids ideally don't come under TRM) that makes total death to 11 out of 26 BMTs and this brings overall thalassemia transplant success rate to around 60% in Haplo identical transplants at Manipal Hospital Jaipur."

24. It is submitted that the children were used in the cruellest and unlawful manner as guinea pigs for testing and that too with the full knowledge that the children were likely to die. This was done for crass commercial interests.

In Italy

25. Petitioner relies on the opinion of Dr. Pietro Sodani, an Italian surgeon who is a leading expert in this field. In a table annexed to a paper written by him and titled "Alternative donor options: Advantages and disadvantages" at Annexure P- 13 page 101 to 118 hereto. He has concluded that the success rate where there is a partial match only, is 58%.

In the USA

26. The clinical trials relating to Haplo SCT procedures began in the USA. Even there these procedures are not approved and are registered as clinical trials.

ICMR Minimum Standard for Haemapoitic Stem Cell Transplantation (HSCT) Units for Blood Diseases

27. The ICMR Guidelines do not allow any hospitals to even apply for approvals for any clinical trial relating to stem cells unless the hospital has already carried out at least 20 allogenic transplants with related match. The guidelines are at Annexure P- 14 page 119 to 121 and the relevant parts are as under:

"1. Patient Volume

e) Criteria for matched unrelated donors (MUD)/ Haplo identical donors and cord blood transplants- the centre must have completed at least 20 allogenic transplants"

Thus the present instance is one of breach of the ICMR Minimum Standard.

28. The National Guidelines for Stem Cell Research, 2013 at Annexure P-15 page 122 to 190 concludes, inter alia, as under:

"Several clinical trials have been carried out using autologous or allogenic CD34+ve hematopoietic stem cells or mesenchymal stem cells (MSCs) in a variety of clinical indications but most of these have been Phase I or early Phase II trials. There is no conclusive proof of safety or therapeutic efficacy of stem cells in any condition yet.

Accordingly, any stem cell use in patients must only be done within the purview of an approved an monitored clinical trial with the intent to advance science and medicine, and not offering it as therapy. In accordance with the stringent definition, every use of stem cell in patients outside an approved clinical trial shall be considered as malpractice. It is hoped that this clear definition will serve to curb the malpractice of stem cell 'therapy' being offered as a new tool for curing untreatable diseases.

7.5 The physician/scientist engaged in stem cell research shall endeavour to avoid any activities that lead to unnecessary hype, or unrealistic expectations in the minds of study subjects or public at large regarding stem cell therapy."

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29. By letter dated 02.06.2018 Ms. Maneka Gandhi, Minister for Women and Child Development wrote to the Minister of Health (at Annexure P-16 page ~ to 19) stating as under:

"Dear Sh. Nadda,

I have received a series of complaints from the family members of patients of Thalassemia who have been treated by Dr. Satyendra Katewa at Soni Manipal Hospital, Jaipur. All these patients were encouraged by Dr. Katewa to undergo Haplo identical HSCT treatment by indicating a high success ratio of 90-95%. Unfortunately in all these cases, the patients expired during the treatment.

2. On receiving these complaints I did some research on the subject and found that even at the most advanced medical institution at USA, the success rate of this treatment is 30%. Therefore what Dr. Katewa promised to the patients was a clear misguidance of a criminal nature. It needs to be appreciated that the family members of the patients suffering from such ailments are in a state of helplessness and therefore become extremely vulnerable when doctors give them a ray of hope. I don't know how much experimental treatments are allowed to be offered in Indian Hospitals and whether there is any mechanism to check their efficacy in the Indian circumstances once they are allowed to be introduced. Unfortunately these treatments are offered only by the high end private hospitals and the patients are fleeced, often with no positive outcomes.

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3. I request you to get their particular matter examined and take necessary action against the doctor and the hospital. Simultaneously, I also request you to have a relook at the system of approving such experimental treatments so that patients are not taken for a ride."

The cases of the petitioners

30. There are two types of cases (i) Thalassemia Major and (ii) Thalassemia Intermedia. In the case of Thalassemia Intermedia (the 8 year old daughter of petitioner no. 3) regular blood transfusions are not necessary as in the case of Thalassemia Major. She was a healthy child as were all the children. Respondent no. 4 persuaded petitioner no. 3 to go in for procedures saying that the petitioner's daughter would die after 2 or 3 years if she does not get the transplant as her condition would worsen. This was the statement made to all the parents. It was in these circumstances and without fully understanding that it was not necessary at all to go in for the procedure that the so called consent was taken. Consent requires full information to be given in writing. Consent requires that the dangerous aspects of the procedure should be clearly spelt out in writing. The cautions should be explicit. The alternative less harmful treatments should be explicit. The fact that the approvals are not taken should have been explicit. The survival rate of about 50% should have been explicit. None of this was done. On the contrary, respondent no. 4 misled the petitioner into believing that approvals were not necessary, that the success rate was above 90%, and that if the procedures were not performed the children would die in a short while. On the contrary, R-4 specifically assured the petitioners that there was

no risk of death. R-4 specifically told the petitioners that the expenses would be in the region of Rs. 8 – 12 lakhs but the actual amounts incurred were very much higher in the region Rs. 40 lakhs to 1 crore and above. The estimate expense quoted to parents of the patients would usually be according to their paying capacity and not the requirements under the treatment. While one parent was quoted an estimate of 10- 15 Lacs, another set of parents were quoted 30 Lacs for the same treatment. The detailed estimates of expenses of the petitioners are marked at Annexure P- /7 hereto including the date of death and the expenses incurred.

Some FIRs registered

Police protect the accused

31. Four of the petitioners filed 3 FIRs against R- 4 and others. They were registered at Vidhyadhar Nagar PS, Jaipur. The details are:

S.I.	FIR No.	Date	Under Section
1.	0325/2018	28.06.2018	304/420/386/120B IPC
2.	0326/2018	29.06.2018	304/386/420/468/120B IPC
3.	0456/2018	25.09.2018	302/304/386/420/468/34/120B IPC

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These FIRs referred to all deaths and trapped parents. The police strenuously resisted the registration of these FIRs and colluded with the respondents. The police have entered into a conspiracy with the respondents to suppress these prosecutions. The respondent no. 4 also file a FIR against Petitioner No. 1 being FIR No. 0137 dated 19.03.2018. In this matter a final report no. 109/2018 (at Annexure P-21 page 231 to 234) was filed in the Magistrate's Court on 15.07.2018.

32. The State is also colluding with the respondents. All the petitioners sent complaints to the state government, govt. of India, MCI Ministry of Health (GOI), PMO and other authorities.

33. The petitioners also made complaints dated 06.08.2018, 23.07.2018, and 17.07.2018 to the MCI and the Rajasthan Medical Council. There was no response. Although the first complaint letter received by Rajasthan Medical Council was on 12.03.2018, the RMC did not take any steps until August, 2018 and tried to dilute the complaints.

34. However, the Medical Council of India wrote to the Rajasthan Medical Council by letter dated 14.08.2018 asking them to take action within a week failing which the MCI would begin proceedings. However, neither the MCI nor Rajasthan Medical Council took any action.

LIST OF DATES AND EVENTS

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Date	Particulars of Events
1940	The Drugs and Cosmetics Act came into force to regulate, usage and import of drugs.
2013	ICMR Minimum Standards for Haemapoitic Stem Cell Transplantations (HSCT) were published. The National Guidelines for Stem Cell Research 2013 state that several clinical trials have been carried out using autologous and allogenic CD34+ve haematopoitic stem cell or mescnchymal stem cell (MSCs) in a variety of clinical indications but most of these have been Phase-I or early Phase-II trials. There is no conclusive proof of safety or therapeutic efficacy of stem cell in any conditions yet.
2014	Petitioner No. 1 met Dr. Satyendra Katewa (R4) for the first time at Magadh Hospital and discussed the same of Krishna Agarwal, his nephew who was suffering from Thalassemia Major.
2015	Petitioner No. 1 met Dr. Satyendra Katewa (R4) at Fortis Hospital Gurgaon, where Dr. Katewa explained to Petitioner No.1 the procedure involved in haplo identical stem cell transplant and assured him that it was a safe procedure with 90-95% success rate.
2015-2017	All the petitioners and several other parents of children suffering from Thalassemia Major met Dr. Katewa (R4) at Fortis Hospital where he told everyone that the procedure was 90-95% safe and that getting this curative procedure

	done would mean their children would be cured completely. Thereafter, multiple people including the petitioners brought their children to Soni Manipal Hospital, now known as Manipal Hospital, Jaipur where the children were admitted and Haplo Identical Stem Cell Transplant was done. As a result of the procedure around 24 children died. This was offered as a therapy to the Petitioners, but in actual, this is still a clinical trial worldwide carried out completely lawlessly, in all probability on behalf of a foreign corporation, and without any of the approvals required under The Drugs and Cosmetics Act, 1940. They were done without taking the informed consent of the petitioners. They were carried out with the knowledge and the understanding that the children would die in the process. When the first child died in 2015 the trials were not discontinued. Even after the children began dying one after the other the trial continued mercilessly without regard for human life.
2018	A paper was recently published in the Paediatric Haematology Oncology Journal in 2018 titled "Allogeneic stem cell transplantation for thalassemia major in India" which stated as under: "There is a lot of interest in haplo-identical stem cell transplantation in the world over the last few years. Novel conditioning and GVHD prophylxis regimens have resulted in dramatic improvements in clinical outcome even without T

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	cell depletion of the graft. There is however very limited data in thalassemia major. In one small series (n=22) using T cell depletion grafts the graft rejection rate was 27% and the TFS about 67%. More recently the use of grafts with depletion of CD3aß T cells looks promising with a few successful reports (44). In a disease where several management options exist and newer ones are on the horizon, whether a treatment option that gives less than -80% TFS can or should be recommended needed further discussion. Haplo-identical SCT therefore cannot be recommended at this time outside the setting of a clinical trial."
25.7.2018	The National Apex Committee for Stem Cell & Research (NAC SCRT) is the Registry in India for all forms of Stem Cell research. As per a recent RTI reply received from the Indian Council for Medical Research (ICMR), it is mandatory for any institute/hospital/entity to register with the NAC SCRT, to be able to conduct clinical trials/therapy, using stem cell for disease/conditions. The response further stated that Manipal Hospital, Jaipur, is not registered with the NAC SCRT.
11.3.2018	In a recent RTI reply received from Government of India, the following was stated: "it is stated that no approval/recognition has been given by this division to the heplo-stem cell transplant for thallasemia affected children."
4.4.2018-7.4.2018	The Directorate of Health wrote to the Registrar, Medical

	Council of Rajasthan to initiate investigation against Dr. Satyendra Katewa and Manipal Hospital, pursuant to which an inquiry committee was formed as Sawai Mansingh Government Hospital. However, they refused to conduct the said enquiry on the ground that they did not have the power and authority to conduct such enquiry against a private hospital or doctor. The committee further informed the Director, Dept. Of Health & Family Welfare, Government of Rajasthan, that the Rajasthan Medical Council was empowered to conduct such enquiry.
28.4.2018	Manipal Hospital responded to an RTI filed with the Government of Rajasthan wherein it stated that the success rate for haplo-identical bone marrow transplant at Manipal Hospital, Jaipur was 60%.
14.5.2018	In a recent RTI reply received from Government of Rajasthan, the following was stated: "the Directorate of Health and Family Welfare, Government of Rajasthan, has not given approval for bone marrow transplant and haplo- stem cell transplant."
2.6.2018	Vide letter dated 2.6.2018, Ms. Maneka Gandhi, Minister of Women and Child Development, Government of India wrote to Ministry of Health & Family Welfare, Government of India, stating that haplo-identical stem cell transplant is an unapproved procedure and Dr. Katewa's actions are of criminal nature and therefore the matter should be examined

	and necessary action should be taken against the doctor and the hospital.
28.6.2018	FIR No. 325/2018 registered at Vidhyadhar Nagar Police Station under sections 304/420/386/120B, IPC, by Petitioner No. 1 & 3.
29.6.2018	FIR No. 326/2018 registered at Vidhyadhar Nagar Police Station under sections 304/420/386/120B, IPC, by Petitioner No. 10.
15.7.2018	FIR No. 0137 was registered by Respondent No. 4 on 19.3.2018 against Petitioner No. 1. A final report No. 109/2018 was filed by the Investigating Officer before the Magistrate Court wherein it is stated that the charges against Petitioner No. 1 are not found to be true and that the complaint made is a false one in retaliation to complaint made by the Petitioner.
6.8.2018 23.7.2018 17.7.2018	The Petitioners made multiple representations and complaints to the Medical Council of India and Rajasthan Medical Council. However, no action has been taken so far.
14.8.2018	The Medical Council of India wrote a letter to the Rajasthan Medical Council asking them to take action within a week failing which the Medical Council of India would begin proceedings. However, no action has been taken so far.
25.9.2018	FIR No. 456/2018 registered at Vidhyadhar Nagar Police Station under sections 302/304/420/386/120B/468/34, IPC, by Petitioner No. 1 & 3.
	The website of Fortis Hospital Memorial Research Institute,

	Gurgaon, states as under: "40% long-term outcome data for haplo-identical transplant"
24/4/19	Hence this petition.

IN THE SUPREME COURT OF INDIA

Civil Original Jurisdiction

Writ Petition (Civil) of 2018

[Under Article 32 of the Constitution of India]

MEMO OF PARTIES

In The Matter of:

1. Amit Kumar Agarwal ... Petitioner No. 1
   S/o. Shri Mohan Lal Agarwal
   R/o. 102, Narayan Plaza,
   Exhibition Road, Patna,
   Bihar-800001

2. Prem Prakash ... Petitioner No. 2
   S/o. Krishna Lal,
   R. of Evergreen House 1-B-14,
   Vikash Nagar, Bundi,
   Rajasthan-323001

3. Sunil Sharma ... Petitioner No. 3
   S/o. Sh Om Prakash Sharma,
   R/o. H. No. 35, M.C. Colony,
   Chanrikhidadri, Haryana-307019

4. Vivek Verma, ... Petitioner No. 4
   S/o. Late R.P. Verma, Resident of 22-C,
   Geeta Bhawan Chauk, Sonipat,
   Haryana- 131001

5. Navneet Kukreja, ... Petitioner No. 5
   S/o. Sh. Krishna Chand,
   Resident of H. No. 416/23, Gali No. 2,
   Ekta Vihar, Kurukshetra,

Haryana

6. Jatinder Sachdeva, ... Petitioner No. 6
S/o. Shri Atam Prakash,
R/o. 228/ Sector-14, Part-2,
Urban Estate, Karnal,
Haryana- 132001

7. Sushil Kumar ... Petitioner No. 7
S/o. Late Sh. Jagdish Kumar,
Resident of 112, Druv Apartment,
GH-9, Sector- 46, Faridabad,
Haryana

8. Lalit Sharma ... Petitioner No. 8
S/o. Sh. Hari Ram Sharma,
R/o. Merchant Road, Jalpaiguri
West Bengal- 735101

9. Alka Sharma ... Petitioner No. 9
W/o. Subhash Chandra Sharma,
R/o. C-502, Saransh Apartment,
34 IP Extension, Patparganj,
Delhi- 110092

10 Kishan Chandrawani, ... Petitioner No. 10
S/o. Late Sri Ramchandra,
Resident of 64/98, Hirapath,
Mansarovar, Jaipur,
Rajasthan

Versus

1. Union of India ... Respondent No.1
Through Secretary,
Ministry of Health and Family Welfare
C Wing, Nirman Bhawan,
New Delhi-110001

2. Manipal Hospital, ... Respondent No.2

Sikar Road,

3

Bidhya Dhar Nagar

Jaipur, Rajasthan-302013.

3. Indian Council for Medical Research, ... Respondent No.3

Through Director General,

V. Ramalingaswami Bhawan,

Ansari Nagar, New Delhi - 110029

4. Dr. Satyendra Katewa ... Respondent No.4

S/O Shri Kehar Singh Katewa ,

House no- 29-A, Ajmera Garden

Kings Road Main , Jaipur

Rajasthan-302019

5. Rajasthan Medical Council ... Respondent No.5

Through the Director,

Sardar Patel Marg,C-Scheme,

Jaipur-302001

Rajasthan

6. State of Rajasthan ... Respondent No.6

Through Additional Chief Secretary,

Department of Medical, Health and Family Welfare,

Jaipur, Rajasthan-

7. Medical Council of India ... Respondent No.7

Through Secretary General,

Pocket- 14 , Sector - 8,

Dwarka Phase -1

New Delhi - 110077

WRIT PETITION FOR VIOLATION OF ARTICLE 21 OF THE CONSTITUTION OF INDIA UNDER ARTICLE 32 SEEKING DIRECTIONS AGAINST THE RESPONDENTS FOR BAN ON ALL ILLEGAL CLINICAL TRIALS PERTAINING TO THALASSEMIA DISORDER USINTG STEM CELL.

TO:

THE HON'BLE CHIEF JUSTICE AND HIS

OTHER COMPANION JUSTICES OF THE HON'BLE SUPREME COURT OF INDIA

THE HUMBLE PETITION OF THE PETITIONER

MOST RESPECTFULLY SHOWETH:

1. The present Writ Petition under Article 32 of the Constitution of India impugns the illegal action of the Respondents as of result of which 24 children have lost their lives in a merciless experiment performed on them in the disguise of curative treatment.

1A. The Petitioner has not approached the concerned authorities for the same reliefs.

1B. The Respondent No. 4 is a private person but is directly involved in the conducting of the unapproved procedure of Haplo Identical Stem Cell Transplant which has caused the death of 24 children.

2. The 10 petitioners are parents of 10 children aged 5 – 18 years who underwent Haploidentical Stem Cell Transplant and most of them died from April 2015 to December 2016 in Manipal Hospital, Jaipur (R-3)

as a result of Heplo Stem Cell Transplant (Haplo SCT) carried out by Dr. Satyender Katewa (R-4). They come from different states of India, i.e. Bihar, UP , Haryana, Rajasthan, Delhi, West Bengal. . This was offered as a therapy, but it is still a clinical trial carried out completely lawlessly, in all probability on behalf of a foreign corporation, and without any of the approvals required under The Drugs and Cosmetics Act, 1940. They were done without taking the informed consent of the petitioners. They were carried out with the knowledge and the understanding that the children would die in the process. When the first child died in 2015 the trials were not discontinued. Even after the children began dying one after the other the trial continued mercilessly without regard for human life. A true typed copy of " Haploidentical Bone Marrow Transplant" published by the Johns Hopkins Medicine, Sidney Kimmel Cancer Centre, year 2018, is marked and annexed herewith as Annexure P-1 (Page 64 to 67).

3. Similar proceedings are reported to be going on in different hospitals in different states of India such as Delhi, Maharastra, Rajasthan, Karnataka, Uttar Pradesh, West Bengal etc. Petitioners, however, are not aware of the position regarding mortality of children and adults in these hospitals in the various states, however, according to the Drug Controller, State of Rajasthan, the percentage of deaths (within 100 days) at Soni Manipal Hospital is comparable to the other hospitals in India. The hospitals in the various states carrying out Heplo SCT procedures unlawfully are, among others, Fortis Research Memorial Institute, Gurugram, Medanta Multi Super Speciality Hospital,

Gurugram, B.L. Kapoor Super Speciality Hospital, Delhi, Dharamshila Cancer Hospital and Research Centre, Delhi, Prem Niketan Hospital, Jaipur, Ruby Hall Cancer Centre, Pune. In view of the unlawful trials being carried out in different states of India, petitioners have filed this writ petition under Article 32 of the Constitution of India for the following reliefs:

iii) for an injunction stopping all Heplo Stem Cell Transplant SCT trials for children with Thalassemia disorder in the country until efficacy is proven.

iv) for the prosecution of those involved in the clinical trials, misleading parents which lead to the death of several children.

Thalassemia

4. Patients with thalassemia do not produce enough hemoglobin (Hb) A ($\alpha 2\beta 2$) because their cells cannot manufacture either the alpha or beta polypeptide chain of human hemoglobin. Alpha-thalassemia depresses only the production of the alpha chains, and beta-thalassemia depresses only the production of the beta chains. Clinically, both alpha- and beta-thalassemia may occur in the major (homozygous), intermediate, and minor (heterozygous) genetic forms and also can interact with the presence of abnormal hemoglobins in the same individual.

5. Haemopoitic stem cell transplantation is the conventional curative option for Thalassaemia patients. This therapy infuses the Thalassaemic patients with stem cells harvested from a compatible donor. If

engraftment occurs, these normal stem cells will then re-populate the recipient's marrow and proliferate to produce normal red blood cells. If the treatment is successful, the patient is no longer transfusion dependent. The sources of stem cells include bone marrow (compatible sibling or matched unrelated donor), cord blood (sibling or cord blood registry) and peripheral blood (sibling or unrelated donor). As families with Thalassaemia tend to have less children, the chances of obtaining a normal and compatible sibling donor (100 % good match HLA) is about 15-25%. However, stem cell transplantation is recommended for patients with compatible sibling donors.

6. Bone marrow transplant (BMT) offers the potential of a permanent cure if a sibling is found to be a HLA compatible donor. The standard conditioning regimen for marrow transplantation in hemoglobinopathies is Buslphan/Cyclophosphamide with or without antithymocyte globulin. Certain experimental groups include total body irradiation as part of their conditioning regimen.

7. The trial is done on persons suffering from thalassemia major/inter media (hereinafter Thalasemia). Thalassemia is a disorder which arises when the red blood cells self destruct at a more than normal rate. The standard treatment worldwide is regular blood transfusion done on regular intervals with medication. This is not a life threatening situation provided regular blood transfusion is available, affordable and is done.

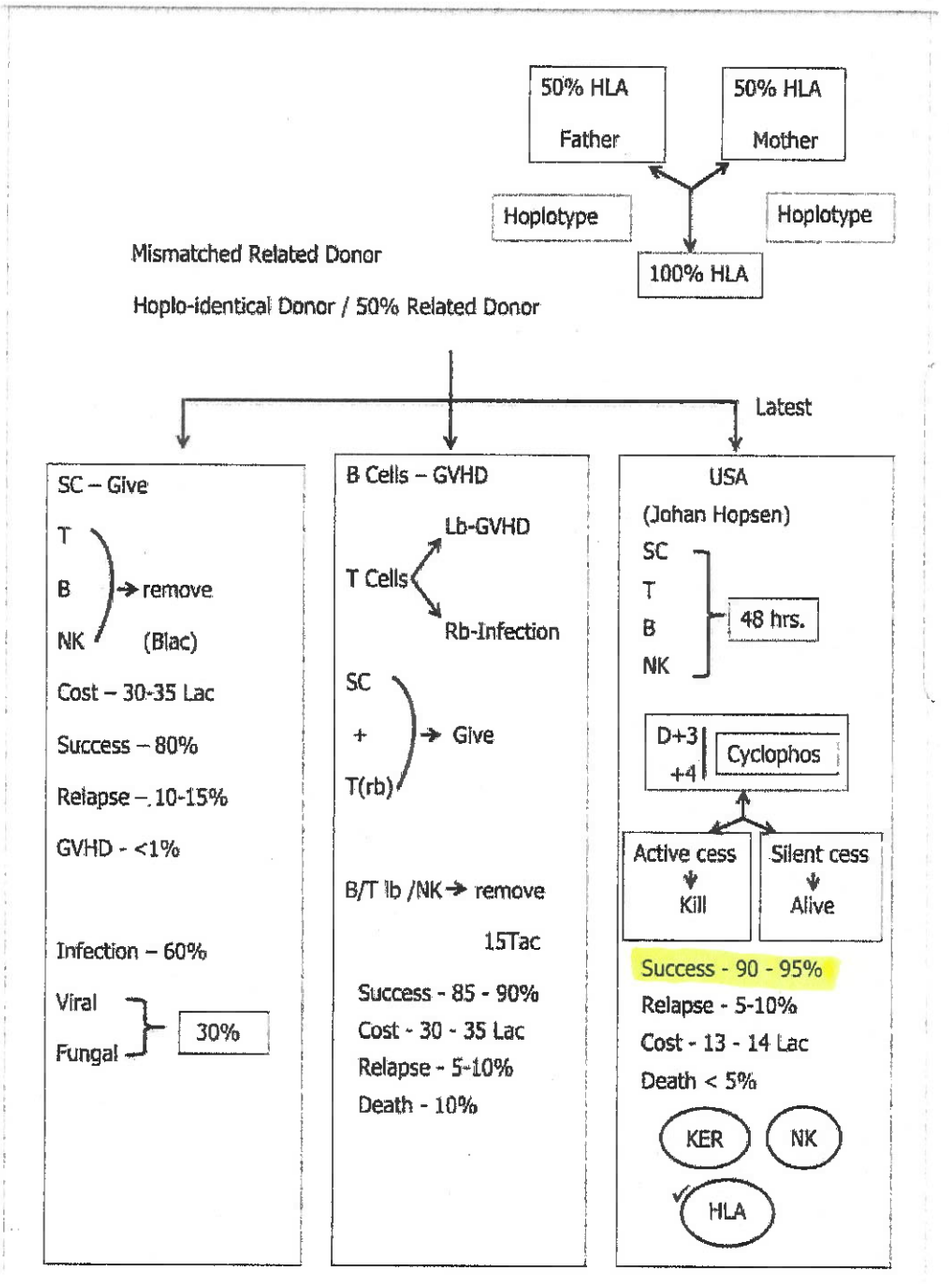
8. Thalassemia is not curable except in a situation where a 100% Human Leukocyte Antigen (HLA) good match is possible between the donor

and the recipient. This is commonly known as stem cell transplant and in common parlance often referred to as bone marrow transplant. Such transplants with a 100% HLA match are well recognised procedure throughout the world as well as in India and the success rate is around 90% where it may be said that Thalassemia is cure. In most other cases there is no cure and the patient has to undergo a lifetime of blood transfusion which is the standard care with negligible life threat.

9. The Heplo SCT trial involves the infusion of stem cells with a less than 100% HLA match with the donor. Such procedures have not been approved by the authorities anywhere in the world as a therapy and are still in clinical trial phases. The question that arises in this petition is whether clinical trials as were done in the present instance were lawful at all.

Informed consent

10. Not only was informed consent not taken, on the contrary the petitioners were misled into believing that the success rate for the trials would be in excess of 90% and also without any risks. This was given by Dr. Satyernder Katewa (R-4) in writing (at Annexure P- 2 (page 68 to —) and a sample is set out herein below:



A true copy of the prescription of Manipal Hospital signed by Dr. Satyendra Katewa, explaining the procedure, dated- Nil, is marked and annexed herewith as Annexure P-2 (Page 68 to —).

11. Petitioners also have an audio recording of the said doctor, a transcript of which and the relevant part of which is as under:

"Petitioner- I have no complaints against you, Sir. I have only two requests. That you tell patients the correct success ratio and cost of the procedure.

Dr. Satyendra Katwa- Look Prem Ji, whoever comes to me I tell them- here are my new patients, there are my old patients. When I told you about the USA paper, at that time there was no available data concerning India. That was when we started. Nobody in India had tried out the procedure by that time. Now, I have data about the 30 patients on which I tried the procedure- now I can tell you what the data concerning India is. Now I tell the patients that the USA paper gives a particular success rate, but it is not applicable in India where the success rate is much lower."

A true copy of the recording of conversation between Petitioner No. and Respondent No. 4, dated – Nil, is marked and annexed herewith as Annexure P-3 (Page 69 to —).

A true typed copy of the transcript of telephonic conversation between Petitioner No. 2 and Respondent No. 4, dated – Nil, is marked and annexed herewith as Annexure P-4 (Page 70 to 72).

Statutory Regime for Informed Consent

12. The statutory regime for obtaining informed consent is set out in Schedule Y of the Act and Appendix V to the Schedule which is as under:

"(4) Informed Consent

(iii)In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject. The Subject's consent must be obtained in writing using an 'Informed Consent Form'. Both the patient information sheet as well as the Informed Consent Form should have been approved by the ethics committee and furnished to the Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

(ii) Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative (a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India). If the Subject or his/her legally acceptable representative

is unable to read/write – an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(iv) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the Informed Consent Form for study Subjects is given in Appendix V.

Appendix V

INFORMED CONSENT

1. Checklist for study Subject's informed consent documents

1.1 Essential Elements:

1. Statement that the study involves research and explanation of the purpose of the research

2. Expected duration of the Subject's participation 535 Drugs and Cosmetics Rules, 1945

3. Description of the procedures to be followed, including all invasive procedures and

4. Description of any reasonably foreseeable risks or discomforts to the Subject

5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.

6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.

7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records.

8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)

9. Compensation and/or treatment(s) available to the Subject in the event of a trial related injury

10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury

11. The anticipated prorated payment, if any, to the Subject for participating in the trial

12. Subject's responsibilities on participation in the trial

13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and

that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled.

14. Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.

15. Statement that in the case of placebo controlled trial, the placebo administered to the subject shall not have any therapeutic effect.

16. Any other pertinent information.

1.2 Additional elements, which may be required:

(a) Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.

(b) Additional costs to the Subject that may result from participation in the study.

.(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.

(d) Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of

the research which may . affect the Subject's willingness to continue participation will be provided.

(e). A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus, if the Subject is or may become pregnant), which are currently unforeseeable

(f) Approximate number of Subjects enrolled in the study

2. Format of informed consent form for Subjects participating in a clinical trial-----

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject Initials: Subject's name:

Date of Birth/Age:

[Address of the Subject

Qualification

Occupation: Student/Self-employed/Service/Housewife/Others (Please tick as appropriate)

Annual Income of the subject

Name and address of the nominee(s) and his relation to the subject (for the purpose of compensation in case of trial related death).]

Place initial

Box (subject)

(i) I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without 'giving any reason, without my medical care or legal rights being affected,

(iii)I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for

scientific purpose(s) Signature (or Representative: ------ Thumb impression) of the Subject/Legally Acceptable

(v) I agree to take part in the above study.

Date: _~/_~/ __

Signatory's Name:

_ Signature of the Investigator:

Date:

Study Investigator's name:

Signature of the witness

Date

Name of Witness:

[Copy of the patient information sheet and duly filled informed consent form shall be handed over to the subject or his/her attendant.]"

In the present case the patients were not informed of their rights before agreeing to undergo a clinical trial (in fact they had no idea that this was an experiment and were given the impression that this was a well established and approved treatment worldwide with negligible risk to the life of their children), and it was only after 60% of the procedure was over were they

given a standard form on which they were told to sign. Copy of that form was not given to them and it remains with the doctor and the hospital. They were given the forms and told to sign in a cursory and mechanical fashion; the forms were taken back on the spot. The parents were not in a position to decline to sign as their children were undergoing the procedures and their immune system was suppressed by the administration of drugs and were the drugs to be discontinued, the children would have died.

13. Referring once again to the statutory regime set out above, petitioners state that informed consent was never taken and was not even attempted, the patients were not covered by medical insurance, they were never informed of the hazards of the clinical trial, they were not told of less hazardous treatments, the cost of treatment at the initial stages was indicated at Rs. 8 – 12 lakhs and the ultimate costs turned out to be Rs. 50 – 60 lakhs per child and some cases the expenses ran into crores of rupees.

The statutory regime for approvals

14. Schedule Y of the Drugs and Cosmetics Act, 1940 lays down the rules and regulations for conducting clinical trials in India. The rules are enumerated as below:

"2. Clinical Trial:

(1) *Approval for clinical trial*

(i) Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under rule 21 (b), and the approval obtained from the respective ethics committee (s). The Licensing Authority as defined shall be informed of the approval of the respective institutional ethics committee(s) as prescribed in Appendix VIII, and the trial initiated at each respective site only after obtaining such an approval for that site. The trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an independent ethics committee (constituted as per Appendix VIII), provided that the approving ethics committee(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.

(ii) All trial Investigator(s) should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol. A qualified physician (or dentist, when appropriate) who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. Laboratories used for generating data for clinical trials should be compliant with Good Laboratory Practices. If services of a laboratory or a

facilities outside the country are to be availed, its/their name(s), address(s) and specific services to be used should be stated in the protocol to avail Licensing Authority's permission to send clinical trial related samples to such laboratory(ies) and/or facility(ies). In all cases, information about laboratory(ies) / facilities to be used for the trial, if other than those at the investigation site(s), should be furnished to the Licensing Authority prior to initiation of trial at such site(s).

(iii) Protocol amendments if become necessary before initiation or during the course of a clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the ethics committee which has granted the approval for the study. No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and the Licensing Authority except when it is necessary to eliminate immediate hazards to the trial Subject(s) or when change(s) involve(s) only logistic or administrative aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Licensing Authority. Administrative and/or logistic changes in the protocol should be notified to the Licensing Authority within 30 days.

(2) *Responsibilities of Sponsor:-*

(i) The clinical trial Sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice (GCP) Guidelines issued by the Central Drugs Standard Control Organization, Directorate General of Health Services, Government of India as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with GCP and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical trial to the Licensing Authority at the prescribed periodicity.

(iii) In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions (Appendix XI), if any, and the reason for

discontinuation of the study or non-pursuit of the new drug application.

[(iv) Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Licensing Authority as referred to in clause (b) of rule 21, the Chairman of the Ethics Committee and the head of the institution where the trial has been conducted, within fourteen days of the occurrence of the serious adverse event.]

(v) in case of injury or death occurring to the clinical trial subject, the Sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever, had obtained permission from the Licensing Authority for conduct of the clinical trial, shall make payment for medical management of the subject and also provide financial compensation for the clinical trial related injury or death in the manner as prescribed in Appendix XII;

(vi) the Sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, shall submit details of compensation provided or

paid for clinical trial

related injury or death, to the Licensing Authority within thirty days of the receipt of the order of the Licensing Authority.]

[(3)(i)] *Responsibilities of the Investigator(s):*

The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII. Standard operating procedures are required to be documented by the investigators for the tasks performed by them. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events. Investigator(s) shall report all serious and unexpected adverse events to the [3][Licensing Authority defined under clause (b) of rule 21, the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their

occurrence. [In case, the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event. The report of the serious adverse event, after due analysis, shall be forwarded by the Investigator to the Licensing Authority as referred to in clause (b) of

rule 21, the Chairman of the Ethics Committee and the Head of the institution where the trial has been conducted within fourteen days of the occurrence of the serious adverse event.]].

[(ii) The Investigator shall provide information to the clinical trial subject through informed consent process as provided in Appendix V about the essential elements of the clinical trial and the subject's right to claim compensation in case of trial related injury or death. He shall also inform the subject or his/her nominees(s) of their rights to contact the Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial for the purpose of making claims in the case of trial related injury or death.]

(4) *Informed Consent:-*

(i) In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject. The Subject's consent must be obtained in writing using an Informed Consent Form'. Both the patient information sheet as well as the Informed Consent Form should have been approved by the ethics committee and furnished to the Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and

submitted to the Licensing Authority before such changes are implemented.

(ii) Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative (a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India). If the Subject or his/her legally acceptable representative is unable to read/write – an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(iii) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the Informed Consent Form for study Subjects is given in Appendix V.

[(iv) An audio-video recording of the informed consent process in case of vulnerabl subjects in clinical trials of New Chemical Entity or New Molecular Entitv including procedure of providing information to the subject and understanding on

such consent, shall be maintained by the investigator for record:

Provided that in case of clinical trial of anti-HIV and anti-Leprosy drugs only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.]

(5) Responsibilities of the Ethics Committee:

(i) It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and well being of all trial subjects. The ethics committee should exercise particular care to protect the rights, safety and well being of all vulnerable subjects participating in the study, e.g., members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, umemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally giving consent. Ethics committee(s)

should get document standard operating procedures'and should maintain a record of its proceedings.

(ii) Ethics Committee(s) should make, at appropriate intervals, an ongoing review of the trials for which they review the protocol(s). Such a review may be based on the periodic study progress reports furnished by the investigators and/or monitoring and internal audit reports furnished by the Sponsor and/or by visiting the study sites.

(iii) In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the Investigator as well as to the Licensing Authority.

[(iv) In case of serious adverse event occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as referred to in clause (b) of rule 21 for conducting the clinical trial, to the

Licensing Authority within thirty days of the occurrence of the serious adverse event.

[5(A). *Serious Adverse Events:-*

(1) A serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalization (in case the study was being conducted on outpatient), prolongation of hospitalization (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening.

(2) The Investigator shall report all serious 3 [***] adverse events to the Licensing Authority as defined under clause (b) of Rule 21, the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurrence as per Appendix XI and the said Licensing Authority shall determine the cause of injury or death as per the procedure prescribed under Appendix XII and pass orders as deemed necessary. [3][In case, the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the

Licensing Authority along with the report of the serious adverse event.

(6) *Human Pharmacology (Phase I):-*

(i) The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into human(s). Studies in this Phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients. Phase I trials should preferably be carried out by Investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the Subjects.

(ii) Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives:-

(a) *Maximum tolerated dose*: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.

(b) Pharmacokinetics, i.e., characterization of a drug's absorption, distribution, metabolism and excretion. Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

(c) *Pharmacodynamics*: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic/ pharmacodynamic studies) may be conducted in healthy volunteer Subjects or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

(d) Early Measurement of Drug Activity: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later Phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

(7) *Therapeutic exploratory trials (Phase II):-*

(i) The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this Phase is to determine the dose(s) and regimen for Phase III trials. Doses used in Phase II are usually

(but not always) less than the highest doses used in Phase I.

(ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

(iii) If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of

sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority.

(8) *Therapeutic confirmatory trials (Phase III):-*

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s). Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drug(s).

(ii) For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).

(iii) For new drugs approved outside India, Phase III studies need to be carried out primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

(iv) If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to the Licensing Authority along with the application.

(9) *Post Marketing Trials (Phase IV):-*

Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but

should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/morbidity studies, epidemiological studies etc."

Bone marrow transplant and Heplo SCT

15. Bone marrow transplant for patients with Thalassemia is well recognised procedure throughout the world and in India. This is performed only when the donor and the recipient have a 100% match. The success rate is approximately 90%. It is an almost safe procedure. The Heplo SCT procedure is not approved anywhere in the world. This is performed when the recipient and the donor have a match that is less than 100%. In the present instances where deaths have occurred the match was 50% onwards but less than 100%. In such a situation no procedure should have been carried out on the children.

16. It is important to note that the children were stable and would continue to be stable for the rest of their lives. All that had to be done was to keep them on medication and regular blood transfusion once or twice a month. Thus, there was no emergency requiring any unapproved procedure or clinical or high risk procedure to be carried out on them. Nor was there any need to carry out a clinical trial on the children.

17. The Monitoring body in the country is the "Indian Stem Cell Transplant Registry" which operates under the Department of Haematology, Christian Medical College, and Vellore. In a paper recently published in the Paediatric Haematology Oncology Journal in 2018 titled

"Allogeneic stem cell transplantation for thalassemia major in India" the conclusion was as under:

> "There is a lot of interest in haplo-identical stem cell transplantation in the world over the last few years. Novel conditioning and GVHD prophylxis regimens have resulted in dramatic improvements in clinical outcome even without T cell depletion of the graft. There is however very limited data in thalassemia major. In one small series (n=22) using T cell depletion grafts the graft rejection rate was 27% and the TFS about 67%. More recently the use of grafts with depletion of CD3aß T cells looks promising with a few successful reports (44). In a disease where several management options exist and newer ones are on the horizon, whether a treatment option that gives less than -80% TFS can or should be recommended needed further discussion. Haplo-identical SCT therefore cannot be recommended at this time outside the setting of a clinical trial."

A true typed copy of "Allogenic stem cell transplantation for thalassemia major in India" published by Department of Haematology, Christian Medical College, Vellore, India dated 09.02.2018 is marked and annexed herewith as Annexure P-5 (Page 83 to 84).

18. It is submitted that the abovementioned Registry is the body which coordinates activities relating to stem cell transplants in India and is the leading authority on the subject. All parties intending to do research or any activity relating to such transplants are required by the central government to register with the "National Apex Committee for Stem Cells and Research". The respondent Hospital has not registered. Evidence of this is a reply dated 25.7.18 received from the Indian Council of Medical Research (ICMR) in response to a query under RTI which is as under:

> "Question: Is Manipal Hospital (old name Soni Manipal Hospital) registered with your body, The National Apex Committee for Stem Cell Research and Therapy Department of Health Research, Govt. Of India?
>
> Answer: No.
>
> Question: Can any organization/institute or Hospital who is not registered with the National Apex Committee for Stem Cell Research and Therapy Department of Health Research, Govt. Of India perform Heplo Stem Cell Transplant and Heplo Bone Marrow Transplant?
>
> Answer: It is mandatory to constitute and register Institutional Committee for Stem Cell Research (NAC SCRT) for any institute/hospital/entity/ institute in Stem Cell Research. The hospital cannot conduct clinical trials/therapy using stem cells for disease/conditions other than listed in Annexure III of National Guidelines."

100%

A true typed copy of RTI response by the Indian Council of Medical Research dated 25.07.2018 is marked and annexed as Annexure P-6 (Page 85 to 87).

19. The website of Fortis Hospital Memorial Research Institute, Gurgaon, has the following on the website :

"40 percent long term outcome data for haploidentical transplant"

A true typed copy of extract of website of Fortis Hospital Memorial Research Institute, Gurugram, dated – Nil, is marked and annexed herewith as Annexure P-7 (Page 88 to 89).

20. The Fortis Hospital Memorial Research Institute, Gurugram further has a video explaining the details of the procedure wherein it is stated that the success rate of Heplo bone marrow transplant is at the moment approximately 50-55%. The relevant extract is reiterated below:

"if it is a match sibling which is ten by ten match it is called match sibling transplant once it does not match it is half match it is called half blow transplant the success rate for a haplo type plant is now in enhancing to fifty to fifty-five percent."

A true copy of the transcript of the video of Fortis Hospital Memorial Research Institute, Gurugram, dated- Nil, is marked and annexed herewith as Annexure P- 8 (Page 90 to —).

21. Similarly, the website of Milaap which does crowd funding for patients who need assistance have a story on their website at and the relevant part is as under:

> "We have been explained that Haploidentical BMT is currently not established as standard of care for Thalassemia Major, and same is carried out in institutionally approved clinical study"

A true typed copy of "Your support could save baby Radhika from lifelong blood transfusion" published by MILAAP, dated- Nil, is marked and annexed as Annexure P-9 (Page 91 to 93).

22. In the case of a 100% match when the donor marrow is inserted in the recipient's body there is an automatic resistance to the foreign substance being injected by the body's immune system. This is overcome by chemotherapy which helps the grafting process by weakening the immune system. Where there is partial match the chemotherapy regime is very intense so as to breakdown the immune system completely. The efficacies of the medicines that are needed to counter act this breakdown have not yet been proved in the world. This is how the deaths took place.

23. In reply to RTI dated 11.3.18 the Government of India stated as under:

> "I am directed to refer to your RTI application dated 29.01.2018 requesting information under the RTI Act, 2005. In So far as NHM-1 section under Ministry of Health and Family Welfare is concerned. It

is stated that no approval/recognition has been given by this division to the Heplo Stem Cell Transplant for Thalassemia affected children."

A true typed copy of the RTI reply by Government of India, dated – 11.03.2018 is marked and annexed herewith as Annexure P-10 (Page 94 to ~).

24. Similarly, in a reply dated 14.5.18 under RTI , the Government of Rajasthan stated as under:

"Question: Kindly inform us if your department has provided/given approval for Heplo Bone Marrow Transplant or Heplo Stem Cell Transplant.

Answer: The Directorate of Health and Family Welfare, Government of Rajasthan has not given approval for Heplo Bone Marrow Transplant and Heplo Stem Cell Transplant."

A true typed copy of RTI reply of the Government of Rajasthan, dated-14.05.2018 is marked and annexed herewith as Annexure P-11 (Page 95 to 97).

25. In response to a RTI filed by Petitioner No. 1, the Sony Manipal Hospital on 28. 04.2018 gave a reply under RTI filled to Govt. of Rajasthan (Dept. Of Health) forwarded to Manipal Hospital, Jaipur instead of responding themself and Manipal Hospital sent bunch of papers to Petitioner. The relevant parts are under:

"Question: Is Haplo indentical Bone Marrow Transplant (BMT) approved by the government?

Answer: Haploidentical transplants are a sub-type of BMT and since in BMT there is no involvement of organs being taken out from donors, and again (putting) implanting in a patient, BMT doesn't come under "Transplant of Human Organ Act", (THOA) 1994. The above act to the best of our knowledge has been amended twice by the government of India in 2011 and 2014 and BMT doesn't come under the scope of this Act which means it doesn't need any approval from Government Agencies."

The abovementioned reply shows that the hospital/doctor has made a false statement to the effect that the petitioners have proceeded with the trial after giving written consent whereas the petitioner has described the manner in which their signatures were taken on a form. The petitioners have also stated that such signatures were taken midway during the trial when they had no option but to continue or else their children would have died. A true typed copy of the RTI response by Soni Manipal Hospital dated 28.04.2018 is marked and annexed herewith as Annexure P- 12 (Page 98 to 100).

26. The reply of the hospital also states that this type of procedure did not require approval which actually was a clinical trial. The reply further states, that the success rate of their Centre was 60% which proves that both the Hospital and the Doctor mislead the families of the patients

with high success ratio of 90-95%. Relevant portion of the RTI reply is stated below:

> "We have done 26 Thalassemia Heplo Identical BMT at Manipal Hospital Jaipur over the last 2 ½ years. Out of 26 Haploidentical BMT, we lost 8 kids due to BMT complications in less than 100 days post BMT (TRM) which makes mortality rate around 30% and BMT success ratio around 70%. Since we have lost 3 more kids after 100 days of BMT(these three kids ideally don't come under TRM) that makes total death to 11 out of 26 BMTs and this brings overall thalassemia transplant success rate to around 60% in Haplo identical transplants at Manipal Hospital Jaipur."

27. It is submitted that the children were used in the cruellest and unlawful manner as guinea pigs for testing and that too with the full knowledge that the children were likely to die. This was done for crass commercial interests.

In Italy

28. Petitioner relies on the opinion of Dr. Pietro Sodani, an Italian surgeon who is a leading expert in this field. In a table annexed to a paper written by him and titled "Alternative donor options: Advantages and disadvantages". He has concluded that the success rate where there is a partial match only is 58%. A true typed copy of "Alternative donor transplant of benign primary hematologic disorders" written by J. Tolar , P. Sodani and H. Symons and published by Macmillan Publishers

Limited, 2015, dated- Nil, is marked and annexed herewith as Annexure P-13 (Pages 101 to 118).

In the USA

29. The clinical trials relating to Heplo SCT procedures began in the USA. Even there these procedures are not approved and are registered as clinical trials.

ICMR Minimum Standard for Haemapoitic Stem Cell Transplantation (HSCT) Units for Blood Diseases

30. The ICMR Guidelines do not allow any hospitals to even apply for approvals for any clinical trial relating to stem cells unless the hospital has already carried out at least 20 allogenic transplants with a 100% matched. The relevant parts of the guidelines are as under:

> "1. Patient Volume
>
> (e) Criteria for matched unrelated donors (MUD/ Heplo identical donors and cord blood transplants- the centre must have completed at least 20 allogenic transplants)"

Thus the present instance is one of breach of the ICMR Minimum Standard. A true typed copy of the relevant extract of the "Minimum Standards for Haematopoitic Stem Cell Transplantation (HSCT) Units for

Blood Diseases, dated- Nil, is marked and annexed herewith as Annexure P-14 (Page 119 to 121).

31. The National Guidelines for Stem Cell Research, 2013 concludes, inter alia, as under:

> "Several clinical trials have been carried out using autologous or allogenic CD34+ve hematopoietic stem cells or mesenchymal stem cells (MSCs) in a variety of clinical indications but most of these have been Phase I or early Phase II trials. There is no conclusive proof of safety or therapeutic efficacy of stem cells in any condition yet.
>
> Accordingly, any stem cell use in patients must only be done within the purview of an approved an monitored clinical trial with the intent to advance science and medicine, and not offering it as therapy. In accordance with the stringent definition, every use of stem cell in patients outside an approved clinical trial shall be considered as malpractice. It is hoped that this clear definition will serve to curb the malpractice of stem cell 'therapy' being offered as a new tool for curing untreatable diseases.
>
> 7.5 The physician/scientist engaged in stem cell research shall endeavour to avoid any activities that lead to unnecessary hype, or unrealistic expectations in the

minds of study subjects or public at large regarding stem cell therapy."

A true typed copy of the relevant portion of the " National Guidelines for Stem Cell Research, 2013" , dated- Nil, is marked and annexed herewith as Annexure P- 15 (Pages 122 to 196).

32. By letter dated 02.06.2018 Ms. Maneka Gandhi, Minister for Women and Child Development wrote to the Minister of Health stating as under:

"Dear Sh. Nadda,

I have received a series of complaints from the family members of patients of Thalassemia who have been treated by Dr. Satyendra Katewa at Soni Manipal Hospital, Jaipur. All these patients were encouraged by Dr. Katewa to undergo Haplo identical HSCT treatment by indicating a high success ratio of 90-95%. Unfortunately in all these cases, the patients expired during the treatment.

2. On receiving these complaints I did some research on the subject and found that even at the most advanced medical institution at USA, the success rate of this treatment is 30%. Therefore what Dr. Katewa promised to the patients was a clear misguidance of a criminal nature. It needs to be appreciated that the family members of the patients suffering from such ailments are in a state of helplessness and therefore become extremely vulnerable when doctors give them

a ray of hope. I don't know how much experimental treatments are allowed to be offered in Indian Hospitals and whether there is any mechanism to check their efficacy in the Indian circumstances once they are allowed to be introduced. Unfortunately these treatments are offered only by the high end private hospitals and the patients are fleeced, often with no positive outcomes.

3. I request you to get their particular matter examined and take necessary action against the doctor and the hospital. Simultaneously, I also request you to have a relook at the system of approving such experimental treatments so that patients are not taken for a ride."

A true typed copy of the Letter by Ms. Maneka Sanjay Gandhi, Hon'ble Minister, Women and Child Development addressed to Shri. Jagat Prakash Nadda, Hon'ble Minister of Health and Family Welfare, dated- 02.05.2018 is marked and annexed herewith as Annexure P- 16 (Pages 191 to —).

The cases of the petitioners

33. There are two types of cases (i) Thalassemia Major and (ii) Thalassemia Intermedia. In the case of Thalassemia Intermedia (the 8 year old daughter of petitioner no. 3) regular blood transfusions are not necessary as in the case of Thalassemia Major. She was a healthy child as were all the children. Respondent no. 4 persuaded petitioner no. 3 to go in for procedures saying that the petitioner's daughter would die

after 2 or 3 years if she does not get the transplant as her condition would worsen. This was the statement made to all the parents. It was in these circumstances and without fully understanding that it was not necessary at all to go in for the procedure that the so called consent was taken. Consent requires full information to be given in writing. Consent requires that the dangerous aspects of the procedure should be clearly spelt out in writing. The cautions should be explicit. The alternative less harmful treatments should be explicit. The fact that the approvals are not taken should have been explicit. The survival rate of about 50% should have been explicit. None of this was done. On the contrary, respondent no. 4 misled the petitioner into believing that approvals were not necessary, that the success rate was above 90%, and that if the procedures were not performed the children would die in a short while. On the contrary, R-4 specifically assured the petitioners that there was no risk of death. R-4 specifically told the petitioners that the expenses would be in the region of Rs. 8 – 12 lakhs but the actual amounts incurred were very much higher in the region Rs. 40 lakhs to 1 crore and above. The estimate expense quoted to parents of the patients would usually be according to their paying capacity and not the requirements under the treatment. While one parent was quoted an estimate of 10- 15 Lacs, another set of parents were quoted 30 Lacs for the same treatment. A true typed copy of the detailed estimates of expenses of the petitioners including the date of death and the expenses incurred dated – Nil, is marked and annexed herewith as Annexure P-17 (Pages 192 to 194).

Some FIRs registered

Police protect the accused

34. Four of the petitioners filed 3 FIRs against R- 4 and others. They were registered at Vidhyadhar Nagar PS, Jaipur. The details are:

S.I.	FIR No.	Date	Under Section
4.	0325/2018	28.06.2018	304/420/386/120B IPC
5.	0326/2018	29.06.2018	304/386/420/468/120B IPC
6.	0456/2018	25.09.2018	302/304/386/420/468/34/120B IPC

These FIRs referred to all deaths and trapped parents. They are at Annexure P- 18 to 20 page 195 to 230. The police strenuously resisted the registration of these FIRs and colluded with the respondents. The police have entered into a conspiracy with the respondents to suppress these prosecutions. The respondent no. 4 also file a FIR against Petitioner No. 1 being FIR No. 0137 dated 19.03.2018. In this matter a final report no. 109/2018 was filed in the Magistrate's Court on 15.07.2018.

A true typed copy of F.I.R No. 0325 of 2018 registered at Vidhyadhar Nagar, dated-28.06.2018 is marked and annexed herewith as Annexure P-18 (Pages 195 to 204).

A true typed copy of F.I.R No. 0326 of 2018 registered at Vidhyadhar Nagar, dated-29.06.2018 is marked and annexed herewith as Annexure P-19 (Pages 205 to 216).

A true typed copy of F.I.R No. 0456 of 2018 registered at Vidhyadhar Nagar, dated- 25.09.2018 is marked and annexed herewith as Annexure P-20 (Pages 217 to 230).

A true typed copy of the Final Report No. 109/2018 in F.I.R no. 0137 of 2018 dated 15.07.2018 is marked and annexed herewith as Annexure P-21 (Pages 231 to 234).

35. The State is also colluding with the respondents. All the petitioners sent complaints to the state government, govt. of India, MCI, Ministry of Health (GOI), PMO and other authorities. The dates and details of the representation letters written to various government authorities is as under:

S.No.	Name	Date	Complain	Department
1	Amit Kumar Agrawal	16.03.2018	Chief Secretary,	Govt. of Rajasthan

			MCI	
		11.03.2018	Chief Minister,NHRC	Govt. of Rajasthan
		20.01.2018	Prime Minister & Health Minister	Govt. of India
		30.04.2018	Meneka Gandhi	Minister for Women & Child Development
2	Prem Prakash	14.02.2018	Health Minister	Central Health Ministry Govt. of India
		15.05.2018	Addl. Chief Secretary	Medical & Health Department Govt. of Rajasthan
		14.02.2018	PMO	Govt. of India
3	Sunil Sharma	11.03.2018	Chief Minister	Govt. of Rajasthan
		10.03.2018	Addl. Chief Secretary	Medical & Health Department Govt. of Rajasthan
		11.03.2018	Chairperson	Rajasthan Human Right Commission
			PMO	Govt. of India
4	Vivek Verma	12.03.2018	Addl. Chief	Medical & Health

			Secretary	Department Govt. of Rajasthan
			PMO	Govt. of India
5	Navneet Kukreja		RHRC, RMC	Govt. of Rajasthan
			PMO	Govt. of India
6	Jatinder Sachdeva	20.03.2018	Addl. Chief Secretary	Medical & Health Department Govt. of Rajasthan
			Chief Minister, RMC	Govt. of Rajasthan
			PMO	Govt. of India
7	Sushil Kumar		PMO	Govt. of India
8	Lalit Sharma (Uncle Sharad Sharma	19.06.2018, 16.10.2018,	CM, PMO, RMC, RHRC Health Ministry	Govt. of Rajasthan
9	Alka Sharma W/o Subhash Chandra Sharma	27.04.2018	Addl. Chief Secretary	Medical & Health Department Govt. of Rajasthan
		27.03.2018	Chief Minister, PMO	Govt. of Rajasthan & India
10	Kishan Chandrawani		Chief Minister	Govt. of Rajasthan

			Addl. Chief Secretary	Medical & Health Department Govt. of Rajasthan
			Prime Minister	Govt. of India
			RMC	Govt. of Rajasthan

36. The petitioners also made complaints dated 06.08.2018, 23.07.2018, and 17.07.2018 to the MCI and the Rajasthan Medical Council. There was no response. Although the first complaint letter received by Rajasthan Medical Council was on 12.03.2018, the RMC did not take any steps until August, 2018 and tried to dilute the complaints.

37. However, the Medical Council of India wrote to the Rajasthan Medical Council by letter dated 14.08.2018 asking them to take action within a week failing which the MCI would begin proceedings. However, neither the MCI nor Rajasthan Medical Council took any action.

38. That it has been more than a year, however, no action has been taken in respect of the three FIRs registered at Vidhyadhar Nagar Police Station, or the multiple complaints and representation letters written by the petitioners to various authorities, including the Rajasthan Medical Council, the Medical Council of India, The Ministry of Health and Family Welfare, Union of India.

GROUNDS

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39. Hence the Petitioners move before this Hon'ble by way of this petition on, inter alia the following grounds:

A. BECAUSE 24 children suffered and died as a result of an unapproved procedure being conducted on them wherein they were treated as guinea pigs in the name of providing curative treatment.

B. BECAUSE Haplo Identical stem cell transplant is an unapproved procedure and cannot be performed unless it is being done as a clinical trial and the trial and the hospital is registered with the NAC(MRT).

C. BECAUSE Respondent no. 4 lied and misrepresented information to the petitioner and other parents like them and informed that Heplo SCT is an approved and safe procedure with 90-95% success rate.

D. BECAUSE the actions of the Respondent No.4 in collusion with Manipal Hospital, Jaipur has resulted in the death of 24 children who suffered immensely because of an unsafe and unapproved procedure being done on them which resulted in their death.

E. BECAUSE Respondent No. 4 extorted money from the petitioners and other such parents in the name of imported medicines as a result of which each of them have spent over Fifty Lacs in the name of curative treatment.

F. BECAUSE the Drugs and Cosmetics Act, 1940 and Rules clearly set out rules and regulations to be followed in cases of clinical trial and it is stated that none of the regulations have been followed.

G. BECAUSE proper consent and information was not provided to the petitioners about the trial as provided under the Drugs and Cosmetics Act, 1940.

H. BECAUSE the petitioners registered three FIRs [FIR no. 0326/2018; 0325/2018 and 0456/2018] at Vidhyadhar Nagar Police Station under Section 302, 304 of IPC, however, so far no arrests have been made, nor any action has been taken.

I. BECAUSE the petitioners have written multiple representation and complaint letters to the Medical Council of India, Rajasthan Medical Council, Ministry of Health and Family Welfare, Union of India and Directorate of Health, Rajasthan Government, however, no concrete actions or steps have been taken so far.

J. BECAUSE this is a case of conspiracy and cold blooded murder of innocent children who were treated as Guinea pigs in the name of providing curative. \

K. BECAUSE respondent no. 4 knowingly persuaded the petitioners to get the procedure done of their children, even children who did not require any curative treatment at all so as to extort money from them, knowing that they would be helpless and bound to

pay any amount asked for by the doctor or the hospital in the name of treatment.

L. BECAUSE respondent No. 4 should be prosecuted for offence committed under Section 302 of the Indian Penal Code and his license should be cancelled so that he may not perform the same procedure on other children.

M. BECAUSE Heplo SCT is being done is multiple Hospitals including Manipal Hospital, Jaipur and the patients and their parents are unaware that the procedure is not approved and is extremely risky with minimal survival or success rates and the process should be stopped with immediate effect.

41. The Petitioners have not filed any other petition seeking the same relief in this Hon'ble Court or any other High Court.

PRAYERS

In light of the facts and circumstances of this case, the Petitioners prays before this Hon'ble Court as under:

A. For a writ of mandamus or any other appropriate writ, order or direction injuncting all clinical trials relating to Haploidentical Stem Cell Transplants in the country until efficacy of the said Heplo Stem Cell Transplant is proven and established worldwide on Thalassemia.

55

B. For an order directing the CBI to take over the investigation and prosecution in respect of FIR 0325/2018, FIR 0326/2018 FIR 0456/2018 Registered at Vidhyadhar Nagar PS, Jaipur and to register further FIRs in respect of the complaints of the remaining petitioners as set out at Annexure P-18 to P-20 page 195 - 238 and to take over the investigations and prosecutions in respect of these FIRs as well.

C. For an order directing the Medical Council of India to take over the enquiries in respect of the complaints of misconduct of the respondents ——— and to complete the enquiries and make orders in accordance with law within 3 months.

D. For any other order/ direction that this Hon'ble Court may deem fit.

AND FOR THIS ACT OF KINDNESS, THE PETITIONER AS IN DUTY BOUND SHALL EVER BE GRATEFUL

Drawn on: 23/4/19 Filed by:

Drawn by: Sneha Mukherjee

Filed on: 24/4/19

SATYA MITRA

Advocate for the Petitioners

IN THE SUPREME COURT OF INDIA

CIVIL ORIGINAL JURISDICTION

WRIT PETITION (CIVIL) NO. OF 2019

(UNDER ARTICLE 32 OF THE CONSTITUTION OF INDIA)

IN THEN MATTER OF:

Amit Kumar Agarwal & Ors. ... Petitioners

Versus

Union of India & Ors ... Respondents

AFFIDAVIT

I, Mr. Amit Kumar Agarwal, aged about 41 years, S/o. Mohan Lal, R/o. 102, Narayan Plaza, Exhibition Road, Patna, Bihar-800001, currently residing in Delhi, do hereby solemnly affirm and swear as under:

1. That I am the Petitioner in the above said case. I am fully conversant with the facts and circumstances of this case and as such I am competent to swear this affidavit.
2. That I have read and understood the contents of synopsis and list of dates on pages B to SS of the accompanying Writ Petition at para 1 to 139 as well as the contents of the accompanying Writ Petition from pages 1 to SS and state that the same are filed under my instructions and the contents thereof are true and correct to the best of my knowledge and belief.

3. That the Annexures to the Petition are true and correct copies of the respective originals.
4. That the Petitioner has not filed any other or similar petition before this Hon'ble Court or before any other Court.
5. That the contents of the accompanying Writ Petition are true and correct to the best to my knowledge and belief and no part of it is false.

DEPONENT

Verification:

Verified in NEW Delhi on the 24th day of April/19 that the contents of the above affidavit are true and correct to the best of my knowledge and belief and nothing material has been concealed there from.

DEPONENT

APPENDIX

DRUGS AND COSMETICS ACT

Schedule Y of the Act and Appendix V to the Schedule which is as under:

"(4) Informed Consent

(i) In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject. The Subject's consent must be obtained in writing using an 'Informed Consent Form'. Both the patient information sheet as well as the Informed Consent Form should have been approved by the ethics committee and furnished to the Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

(ii) Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative (a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India). If the Subject or his/her legally acceptable representative is unable to read/write – an

impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(ii) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the Informed Consent Form for study Subjects is given in Appendix V.

Appendix V

INFORMED CONSENT

1. Checklist for study Subject's informed consent documents

1.1 Essential Elements:

1. Statement that the study involves research and explanation of the purpose of the research

2. Expected duration of the Subject's participation 535 Drugs and Cosmetics Rules, 1945

3. Description of the procedures to be followed, including all invasive procedures and

4. Description of any reasonably foreseeable risks or discomforts to the Subject

5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.

6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.

7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records.

8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)

9. Compensation and/or treatment(s) available to the Subject in the event of a trial related injury

10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury

11. The anticipated prorated payment, if any, to the Subject for participating in the trial

12. Subject's responsibilities on participation in the trial

13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled.

14. Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.

15. Statement that in the case of placebo controlled trial, the placebo administered to the subject shall not have any therapeutic effect.

16. Any other pertinent information.

1.2 Additional elements, which may be required:

(a) Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.

(b) Additional costs to the Subject that may result from participation in the study .

.(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.

(d) Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may . affect the Subject's willingness to continue participation will be provided.

(e). A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus, if the Subject is or may become pregnant), which are currently unforeseeable

(f) Approximate number of Subjects enrolled in the study

2. Format of informed consent form for Subjects participating in a clinical trial-----

Informed Consent form to participate in a clinical trial

Study Title:

Study Number: 62

Subject Initials: Subject's name:

Date of Birth/Age:

[Address of the Subject

Qualification

Occupation: Student/Self-employed/Service/Housewife/Others (Please tick as appropriate)

Annual Income of the subject

Name and address of the nominee(s) and his relation to the subject (for the purpose of compensation in case of trial related death).]

Place initial

Box (subject)

(i) I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without 'giving any reason, without my medical care or legal rights being affected,

(iii)I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any

further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) Signature (or Representative: ------ Thumb impression) of the Subject/Legally Acceptable

(v) I agree to take part in the above study.

Date: _~/_~/ __

Signatory's Name:

_ Signature of the Investigator:

Date:

Study Investigator's name:

Signature of the witness

Date

Name of Witness:

[Copy of the patient information sheet and duly filled informed consent form shall be handed over to the subject or his/her attendant.]"

(TRucby)

ANNEXURE P-1

Haploidentical Bone Marrow Transplant

Drs. Heather Symons and Ken Cooke

The lack of adequate bone marrow donors to match the needs of patients was the inspiration for Johns Hopkins scientists who pioneered haploidentical bone marrow transplant (BMT). This breakthrough discovery makes bone marrow transplant possible for nearly every patient who needs the treatment.

In haploidentical BMT, parents, siblings, and potentially aunts and uncles, nieces and nephews, half-siblings, and grandparents can safely serve as donors. Our experts have performed more than 500 hapliodidentical transplants for adult and pediatric leukemia and lymphoma with safety and toxicity comparable to traditional transplants. This safety has made it possible for this type of BMT, available only at Johns Hopkins, to be used to treat many types of cancer and non-cancerous pediatric diseases:

- pediatric hematologic malignancies
- pediatric solid tumors, to induce a graft vs. tumor effect and reduce recurrence in high-risk cancers.
- sickle cell anemia
- immune diseases
- in conjunction with solid organ transplants to prevent organ rejection and eliminate the risks and costs associated with lifelong treatment with immunosuppressant drugs.

Haploidentical Bone Marrow Transplant Clinical Trials

Pediatric bone marrow transplant expert Heather Symons is directing a clinical study of haploidentical bone marrow transplant for patients with refractory and/or relapsed high-risk leukemia and lymphomas. The study is available only at Johns Hopkins. Symon's novel trial uses half-matched donors and, therefore, is an option for almost any patient where BMT is indicated. The safety and toxicity of haploidentical bone marrow transplants performed to date is comparable to matched transplants. As a result, the strategy is now being used in earlier treatment of pediatric leukemias and lymphomas, and has been expanded to include children with solid tumors, such as sarcoma and neuroblastoma to incite a graft versus tumor effect and prevent cancer recurrence.

Haploidentical BMT Clinical Trials:

A phase II trial of partially HLA-mismatched (HLA-haploidentical) bone marrow transplantation for high-risk solid tumors.

Purpose:

Allogeneic hematopoietic stem cell transplantation (HSCT) may be associated with a clinically significant "graft-versus-tumor" (GVT) effect, even against disease that is unresponsive to chemotherapy and radiation therapy. Graft-vs.-tumor (GVT) effects have been described after allogeneic HCT for neuroblastoma, Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, melanoma and hepatoblastoma.Our goal is to maximize a T cell and NK cell mediated graft versus tumor effect in poor prognosis solid tumor patients using haploidentical donors, T cell replete bone marrow, and a unique post-

transplant immunosuppression regimen containing post transplantation Cy and an mTOR inhibitor. This therapy will be widely applicable because almost all patients have a half-matched donor available (parent or sibling). We hope to demonstrate the safety and feasibility of this therapy in anticipation of combining this platform with additional post-transplantation therapy such as cryoablation, Donor Lymphocyte Infusion (DLI), stem cell directed therapy, immunologic checkpoint inhibitors, and/or metabolic inhibitors.

A Pediatric Blood and Marrow Transplant Consortium (PBMTC) multi-center Phase II Pilot Trial of Myeloablative Conditioning and Transplantation of Partially HLA-mismatched T cell replete Bone Marrow with post-transplantation cyclophosphamide for Pediatric Patients with Hematologic Malignancies

Purpose:

We propose a multi-institutional phase II study in children with high-risk leukemias in 1st CR, acute leukemias in 2nd CR, MDS, and JMML. The myeloablative conditioning regimen prescribed will be TBI-based for lymphoid leukemias and busulfan-based for myeloid leukemias, or for lymphoid leukemias in which a TBI-based regimen was used for the first transplant. Our goal is to establish an easily exportable, inexpensive platform for haplotransplantation that has a safety profile equivalent to matched related and unrelated BMTs. The primary objective will be to estimate the incidence of 6-month non-relapse mortality, hypothesizing that NRM is less than 18%.

Bone Marrow Transplantation and High Dose Post-Transplant Cyclophosphamide for Chimerism Induction and Renal Allograft Tolerance

Purpose:

Kidney transplantation is a good treatment for people with end-stage kidney disease. However, there is still much to learn about how to best care for the transplanted kidney and keep it working for a long time. Unless a person receiving a kidney from someone else takes drugs that reduce immune function, the kidney will be rejected. Those drugs must be continued life-long. The side effects of these drugs cause many problems, including infections and cancer, and frequently shorten life. Long term immunosuppressive medications do not entirely protect against rejection episodes. Rejection episodes can cause the long term weakening and loss of the transplanted kidney from cumulative chronic rejection effects. ï¿½The likelihood that a transplanted kidney will still be functioning at 10 years is only about 50%. Both the quality and duration of life are reduced on dialysis, and the risks of transplantation increase with subsequent transplants due to sensitization. Life expectancy after a second or third kidney transplant is even shorter. For all these reasons, tolerance of the transplanted kidney, without chronic rejection and without the need for permanent immunosuppressive drug treatment, is a highly desirable goal. If this can be achieved, it would make "one kidney for life" possible.

Eligibility:

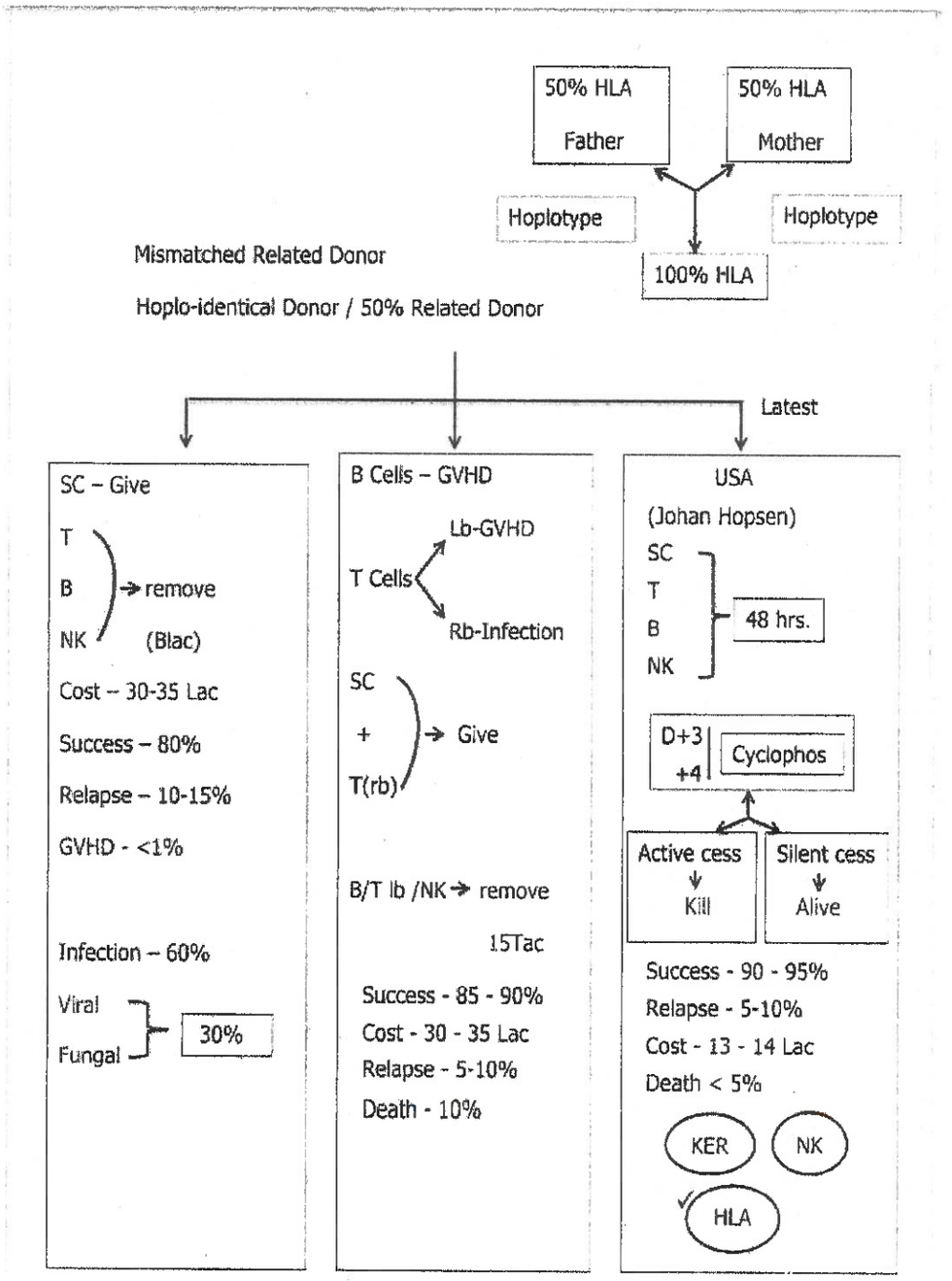
Patients between the ages pf 18 to 65 years old who are the recipient of a first renal allograft from an HLA-haploidentical, living related donor.

(True copy)

ANNEXURE P-2

MANIPAL

HOSPITAL **OUT PATIENT RECORD**



(TRW Co Pn)

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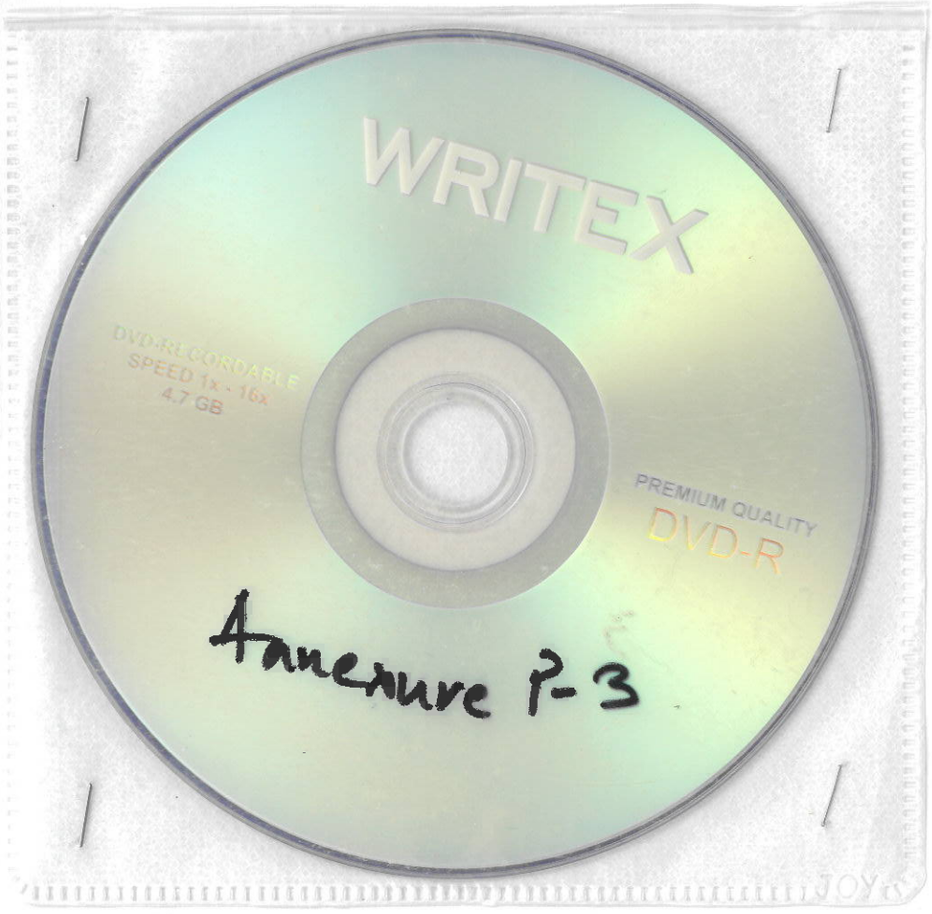
ANNEXURE-P/3



(True Copy)

ANNEXURE P-4

OFFICIAL TRANSCRIPTION

P- Good evening

K- Tell me

P- We'll come for the routine check-up in a week

K- Ask me 2 days before coming. Because of the letters that you have written, I have been answerable to a lot of people, and have been travelling a lot as a result.

P- We'll come after confirming the date. We'll come only when you tell us to.

K- Yes, as I said, I've had to go to several places because of all the letters and emails that you have been writing against me.

P- Don't worry, I'll only come when you're free.

K- If I'm not there, you can always meet Ramzan- there's no problem

P- I will confirm on WhatsApp before coming

K- No, please don't WhatsApp me, I get a lot of messages on WhatsApp. I have already told you before, you are Naresh's *jijaji*, you can always call me.

P- Sure, Sir, I will call and confirm before coming

K- I usually don't check WhatsApp properly, I only open it and close it. So I often miss the messages. You are Naresh's *jijaji*, you can call me whenever

you need- there's no issue. I get more than 1000-1200 messages, I'm unable to check and read all of them.

P- Okay Sir, this time I'll be careful. I will call and confirm before arriving

K- At this time, all of you have troubled me so much.

P- Yesterday I received a call from a sales tax officer

K- Sales tax officer?

P- Yes. You must have told him to call me.

K- You must be crazy. I don't do these things. You are Naresh's *jijaji*, it is unfortunate that you don't know me even this much. It's been 5-6 months that you've been with me, and you still don't know me. For those parents who have actually lost their children due to the procedure, they are obviously sad and distraught- there's nothing I can do about that. I'm telling you, even if Amit Ji comes crying back to me, I will be there to help him. Even if Amit Ji wants to destroy my life, even after that when he comes back crying to me, I will be there to help him. You have not understood me. It saddens me to see that you can even write such things about me. I am unable to understand why someone for whom I have spent sleepless nights and for whom I have worked so hard, would blame me for robbing them off their money, murdering their children, and lying to them.

P- I got a call from the CTO yesterday

K- If you are saying something to someone and they take advantage of it, that's wrong. But I do not do such things in my life.

P- Sir, I only know one thing- I was told by the CTO that he got a call from a Jaipur doctor and he is calling me regarding this issue.

K- Prem Ji, listen to me. You are Naresh's *jijaji*. Even if you were not Naresh's *jijaji*, I would still not do this. What are you talking. You 5-7 people are ganging up against me. You think I can't do anything? But I am only sitting quiet because everybody has the right to raise a voice. I do not do these immoral things, rest assured.

P- Sir, you must have called up the Tarun yesterday and spoken to him- that's whyhe came to me.

K- Who is Tarun?

P- Bhagya Rathore's *taoji*.

K- Oh yes I spoke to him. What happened to him? Why is he saying such things about me?

P- You must have called him up to ask him where his shop is.

K-Could I not have found that out on Google within a minute? What are you talking? Why would I need to call anybody up for that?

P-I'm telling you the reality, Sir.

K-Tarun's shop is one of his kind in the area (Boondi), right?

P-Yes

K- See? Could I not have found it out very simply on Google? Why would I take the trouble of calling up and asking him? Understand what I am saying. You might have some grievances against me.

P- No Sir, I have nothing against you. I have only respect for you.

K- Don't say that. I have the e-mail that you sent to *madam*, and I know what you feel about me. I am giving you my answer to that e-mail now. I have told

you before as well Prem Ji- the counselling paper that I give to you people, I give that paper today also.

P- Sir, I have had only one request from you. That you should tell people the correct success ratio, and the correct cost of the procedure. I have no other intention.

K- Listen to me. We are answerable. Thus, we have taken out all the data. We have taken out all the bills of the transplant. People have gone home having spent only 7 lakhs, 9 lakhs.

P- Sir, even the German medicines themselves are costlier than that.

K- You are telling me that I'm ripping you off your money based on German medicines? You are the ones who are ordering the medicines. It is wrong for you to blame me for this.

P- Sir, this money is not even enough to buy Thiotepa.

K- You are the ones who are ordering Thiotepa, right? Tell me something. I only tell you the cost of the transplant and the BMT, right? After that, when you say you want so many medicines like Theosulfan and Thiotepa etc etc, do you expect me to bring these medicines from my house? Obviously you will have to bear the cost for these medicines. Understand what I'm saying. When I began the Thalassaemia transplant, the 90% success rate that I told you about, is from a USA paper. In every counselling, I mentioned Germany, USA, Europe- these are merely papers. These papers are not regarding Indian patients, right? They don't determine the success rate for Indian patients. In India, even for a 100% match transplant, the success rate is 55% for high-risk patients. Now tell me something. How is the outcome better for you Rajasthan people?

P- I don't know that, Sir. But you never made this high-risk low-risk distinction to anybody.

K- You should have asked me! Listen to me. Because you provided your child with high quality blood and high quality iron chelation- the whole problem arises when you provide blood from the filter.

P- Sir, that is a separate discussion. But you never made the high-risk low-risk distinction to any of the patients.

K- What are you talking? Everything is told to the patients. I sat with you for one and a half hours, twice. One and a half hours is very valuable in a doctor's life. And then you blame me for the cost of German medicines. You are the ones who order the medicines, you are the ones who get the import licenses issued, and then you say I'm doing this for the money.

P- But at least you told us to buy the Tajaji (8:14)medicine right?

K- You were the ones who payed the money for the medicine, you were the ones who collected the bills for the medicines, you did everything. My role was only to give the prescription- after that whatever you do is your responsibility. I give prescriptions today as well. Look Prem Ji, you are Naresh's *jijaji*, otherwise I would not even have taken the trouble to explain this to you. I am taking this trouble because I consider your wife to be like a sister to me.

P- Okay, Sir

K- I am the type of person that does *puja* twice a day. Prem Ji, when I have conducted 100% matching transplants, even to those patients, I have never cited a success rate of more than 70% for Indian patients. For the Haplo

transplant that you got done for your children, the USA paper on the basis of which you got the transplant done, cited a 90% success rate. That data was not for India. I don't even tell the 100% matching patients that they will have a 90% success rate. I'll tell you one more thing, Prem Ji.

P- Yes, Sir

K- Look, one Lord is sitting up there. Right?

P- Yes Sir, the Lord is higher than anybody.

K- Whatever happens, you can't tarnish the truth. The truth will always remain the truth. 9:38. CONFIRM

P- That's exactly what I'm saying.

K- When I take your consent, forget about the success rate, regardless of the percentage whether it is 70% or 90%- I write that there is no guarantee of transplant.

P- That isn't written anywhere, Sir.

K- You signed the form that said this.

P- You got that signed only a day before getting admitted in BMT.

K-This is not an easy task. Even though the form is signed one day before the actual procedure, patients have the choice of not signing the form and withdrawing from the procedure. I assure to these patients that full recovery will happen. If they do not want the procedure conducted, I am completely fine with it. If they ask me whether the procedure is dangerous- Of course it is dangerous! If it wasn't dangerous, everybody would've gotten cured, and it would've been conducted everywhere. Of course it is a dangerous procedure. So until the main transplant is commenced, the procedure can be stopped. And

I have personally discharged 3-4 patients by stopping the procedure in this manner. It doesn't work like this, Prem Ji. I worked for your child. I conducted the transplant on 30 children. Of them, 20 are fine. Do you know that only deaths within the first hundred days are considered to be deaths caused by the BMT procedure? After 100 days, the death is considered to be unrelated to the procedure. Personally, I still consider those patients who die after the hundred-day period, thinking that it is still a loss. However, as per science and data, those patients would not be considered. Today, you are not seeing the 20 children who survived- you are only look at the 10 who died and creating an unnecessary hue and cry about it. This is wrong, Prem Ji.

P- I have no complaints against you, Sir. I have only two requests. That you tell patients the correct success ratio and cost of the procedure.

K- Look Prem Ji, whoever comes to me I tell them- here are my new patients, there are my old patients. When I told you about the USA paper, at that time there was no available data concerning India. That was when we started. Nobody in India had tried out the procedure by that time. Now, I have data about the 30 patients on which I tried the procedure- now I can tell you what the data concerning India is. Now I tell the patients that the USA paper gives a particular success rate, but it is not applicable in India where the success rate is much lower.

P- But the reality that we watched before our own eyes is true, right? You can't deny that.

K- The patients that you saw were cancer patients. They did not even undergo transplantation. I am also a cancer doctor. So I get all types of patients, even cancer patients. I have all the lists and names.

P- I have only one request from you, Sir. That you tell the correct success ratio and cost, so that the patient comes mentally and physically prepared accordingly.

K- Prem Ji, ask the patients who have been admitted. I have given dates to 15 children. 8 children, 30%, overall 60-65%, I still say this right? (12:58 to 13:19 omitted. Ask someone).But now I tell my patients clearly, that the old data regarding the rest of the world gives a particular success rate, while the Indian data is separate. But that's not the point. The point is that unwillingly, you and I have developed a relationship because you are Naresh's *jijaji*. Prem Ji, you are an emotional person. You are unable to see beyond a particular level. That is why you are being misused. You are unable to see it. And I don't have a problem with you about this. Even after so many people have spoken to me against you, I have always given you the benefit of doubt because I know that you are an emotional person and because we have such a relationship. The only thing I am telling you, Prem Ji, is that these people are using you- nothing else. If you come to me, I will give you the list of the 44 patients with their phone numbers. You can check for yourself, who all are alive and who aren't. It's that simple.

P- Sir, I beg only one thing of you. If a new patient comes to you, please tell him the correct success ratio and cost of the procedure. I am not concerned with anything else.

K- Listen to me, Prem Ji. I'll tell you right away. But before, there was no available Haplo data to tell. In India, the Haplo transplant for thalassaemia patients is taking place only in nine centres. Of these nine, our data is the best.

P- There is no doubt that there is no one better than you in the country, Sir.

K- Our data is the best in India. This means that in India, if you want a transplant for a high-risk patient, then the success rate does not exceed 50-60%. And if you want a transplant for a low-risk patient, then the success rate is 80%, as per our own data. As per our data, ten of the children are low-risk patients.

P- Sir, that is what I am requesting you. Please make the low-risk high-risk distinction clear to the patients. There is no other problem.

K- But I will first have to try the procedure on 25-26 children, and only after that can I make this distinction and provide the data. How can I tell you before testing it? When I started out, I told you what I knew. I told you what the paper said. Only when I perform the tests will I be able to provide the data.

P- Sir, I have no such complaints against you and will always be indebted.

K- Prem Ji, I am only troubled because I know and my soul knows what I did. Maybe due to issues with your understanding, I have had to explain it several times.

P- The only thing that saddens me is that tomorrow more parents can lose their children in the same manner. So the only thing that I wish for is that you only tell the patients the truth.

K- Tell me one thing. Did I not cure Krishna and send him back home? Despite that, he died. But that had nothing to do with the transplant. Now what should we do? Tell me. You can't change destiny. Prem Ji, you and I are both human beings- we cannot change destiny. Do not forget that. Look, for 16 months after the transplant, everything was okay and he was healthy, right? Then suddenly the death occurred. How can I be held responsible for this, which Amit Ji is standing up against me for? Only if the death occurs within

hundred days from the date of the transplant can we say that it was caused by the transplant. Moreover, this procedure is not risk-free. This is not like an appendix operation, where there is no risk involved.

P- Right

K- Now you are blaming me for deaths occurring 16 months after the procedure also. I am not God that I can change everything.

P- Sir, even today I have only one request. That you tell the truth about the success ratio and cost, so that parents of thalassaemic children can be mentally prepared, and can understand that they are giving an informed consent about choosing to undergo or not undergo the procedure.

K- Now I refuse the demands of the thalassaemic patients. I tell them that I will not perform the transplant. They ask me why. I tell them because the success rate is only 70%. They start crying thinking that I have a personal feud against them. They tell me that they have no other choice and that their kid will die anyway.

P- But Sir, the kid will not die. These patients will survive at least till the age of 45, right?

K- That is only because you got it done well in advance. What I am saying is that those families crib in front of me saying that they won't be able to find a girlfriend or a boyfriend for their children. You should see especially how the older kids talk.

P- Sir that is what I'm saying. That you tell them the truth so that they can be mentally prepared and make an informed decision as to whether or not to undergo the procedure.

K- Prem Ji, that is exactly what I say. But should I tell you what happens then? I'll explain something to you. I have never told this to anyone. But, Prem Ji, you know what happened with Krishna, and how my relationship is with Amit Ji. Do you know how many years Amit has been in touch with me?

P- I don't know that. You would know it.

K- I'll tell you. Since 2011.

P- Oh

K- He's been in touch with me since 2011.

P- Yes

K-He knows everything. So why is he not taking the chance? Because every time he meets me I tell him that the situation is dangerous and risky. Ultimately what happened is that his fear won. I did everything. I cured his child and sent him back home. You have seen so many transplants. Have you seen even one such case where the patient has returned home without a 5-7-day complication? No, right?

P- I understand that. In fact, some patients have complications even till 1-1.5 years after the transplant.

K-20:11 to 20:16 omitted. Everything was okay, there were no issues. Medicines also stopped and eating was also fine. What I am trying to explain to you is that there are some families for whom the 35-40 years age limit as a result of the disease, is acceptable. For some other families it is completely unacceptable. You know about Sunil Sharma Ji?

P- Yes

K- What was the name of his child?

P- The one with Intermedia

K- Yes. You know what he said? I told him that there were complications in the first cycle, and that there are complications with his child. He may deny this now, but God is watching. He told me that once he dies, there is no one to take after his unmarried daughter- not even a sibling. He said that he will have to take the risk of undergoing this transplant procedure on his child, or he will die with the burden that there is nobody to take care of his daughter. He also came to me through references from my doctor friends.

P- Sir, this you and him only know, what was the conversation between you two.

K- What?

P- Only you and Sunil Ji know what conversation happened between you two.

K- That's not what I'm explaining to you. I'm only trying to explain to you, that there are some families who are willing to take the risks even after having full knowledge of the risks. They are adamant on getting the cure.

P- But all families don't understand this, right? Confirm this. 21:38

K- Of course they understand.

P- Today also, I have only one request from you.

K- Tell me one thing. What did you understand when you came?

P- You told me that the success ratio is 90-95%, so that is what I understood.

K- So you came with the understanding that the ratio is 90%?

P- Definitely, Sir. I came with the understanding of 90-95%.

K- Listen to me, Prem Ji.

P- Yes

K- If you were part of the 10%, then what?

P- Sir, that 10% risk exists even for an appendix operation.

K- Then for you it would have been 100% right? I would have been, right?

P- Sir, anybody would be willing to take a 5% risk.

K- What are you talking. It would have been, right? It would. Never mind, inform me before coming. You are an emotional person and you are being misused- that is all I wanted to say to you. Nothing else.

P- Sir as I have said, I have only one request from you. Rest assured, I'll do anything for you.

K- Just don't ruin me. That's all I ask of you.

P- I will do anything you say Sir. I have only this one request from you. Nothing else.

K- No problem.

P- Okay. Thank you Sir.

K- Okay, bye.

True copy

ANNEXURE P-5

Paediatric Hematology Oncology Journal 1 (2017)114-120

Contents lists available at Science Direct

Pediatric Hematology Oncology Journal

Journal Homepage: hppts//www.elseviour.com/journals/pediatric-hematology-oncology-journal

Allogeneic stem cell transplantation for thalassemia major in India

Vikram Mathews, Poonkuzhali Balasubramanian, Aby Abraham, Biju George, Alok Srivastava

Department of hematology, Christian Medical College, Vellor, India

Article history: Received 14 October, 2017. Received in revised form 1 February 2018. Accepted 1 February 2018. Available online 9 February 2018.

Keywords:

Thalassemia major. Allogeneic stem cell transplant. Conditioning regimens. Regimen related toxicity. Alternative donors.

Abstract

Allogeneic stem cell transplantation (allo-SCT) is the only currently available curative treatment for thalassemia major. Since it was first done in 1981, several thousand patients have benefitted from it and it is now possible to ffer this treatment in different parts of the world with good results. With better risk stratification and supportive care, the results of allo-SCT are now very good even in high risk patients who have significant iron overload related organ dysfunction. The improvements have mainly been in the conditioning strategies with less toxic myeloablation and management of the complications of SCT. However, several challenges remain. Transplant related complications still cause

significant morbidity and mortality. There is data to show that the results of transplantation as best if done in well transfused and chelated patients <years of age. as only a third of the patients will have a matched related donor, there is need for investigating SCT with alternative donors. Experience with SCT for thalassemia major from matched unrelated donors or haplo-identical donors is still limited byt needs further exploration. Adequate management need to be provided psot-SCT for all pre-existing complications particularly iron chelation to prevent further organ dysfunction. Systematic follow up is needed to measure long term outcomes. The biggest challenges in India re the cost of this treatment and access to centres capable of providing this treatment. With greater support from the government, health insurance and philanthropic programs, there has been a rapid increase in the number of SCTs for thalassemia major in India. The number of centres providing this treatment are also increasing making this curative treatment more widely available in India.

6.3. Haplo-identical stem cell transplants

There is a lot of interest in haplo-identical stem cell transplants in the world over the last few years. Novel conditioning and GVHD prophylaxis regimens have resulted in dramatic improvements in clinical outcome even without T cell depletion of the graft. There is however, very limited data in thalassemia major. In one small series (n=22) using Tcell depletion grafts the graft rejection rate was 27% and the TFS about 67%. More recently the use of grafts with depletion of CDaB T cells looks promising with a few successful reports [44]. In a disease where several management options exist and newer ones are on the horizon, whether a treatment option that gives less than -80% TFS can or should be recommended needs further discussion. Haplo-identical SCT therefore cannot be recommended at this time outside the setting of a clinical trial.

(TKB Copy)

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ANNEXURE P-6

TRUE TRANSLATION

INDIAN COUNCIL OF MEDICAL RESEARCH
DEPARTMENT OF HEALTH RESEARCH
(MINISTRY OF HEALTH AND FAMILY WELFARE)

V. RAMALINGAWAMI BHAWAN, ANSARI NAGAR,
PSOT BOX 4911, NEW DELHI – 110029

FILE NO. 23/44/2017-B.N.S. Dated 25.07.2018

To

Shri Prem Prakash Kishanchand
Evergreen House, 1-B, 14,
Vikas Nagar, Bundi 323001,
Rajasthan

SUB Request for Supply of Information under Right to Information Act, 2005

Sir,

Concerned to the aforesaid subjected matter regarding supply for information under RTI Act, vide letter No. 160/CP-RTI/2018/ICMR dated 24.07.2018, given in following paras:

Que: National Apex Committee for stem Cell Research and Therapy Department of Health Research Govt. of India concerned to the your department which one or how

many hospital made registration under the centre, you are requested to furnish the photocopy of the list of the hospital that is enrolled and Name & Registration of the Hospital.

Ans. The said information is available there at website of NAC-SCRT

Que. National Apex Committee for stem Cell Research and Therapy Department of Health Research Govt. of India concerned to the your department which one or how many hospital made registration under the centre there in Rajasthan and/or Manipal Hospital (earlier Soni Manipal Hospital)? You please explain about registration number and date.

Ans. Not available

Que. National Apex Committee for stem Cell Research and Therapy Department of Health Research Govt. of India concerned to your department , how many branches that is registered in State, they are bounded to registered for the same service or for separate, either yes or no?

Ans. No.

Que. Either organization or hospital was not registered with the department of the National Apex Committee for stem Cell Research and Therapy Department of Health Research Govt. of India, please to explain about the Hospital can made the Hello Steam of cell transplant or Helpo Bone Transplant to be conducted or not please give the information?

Ans. It is mandatory to continue and register Institution Committee for stem Cell Research with NAC-SCKT and for any institution / Hospital / Entity institute in stem cell research. The Hospital cannot conduct clinical other than listed in Annexure III of National Guidelines.

Yours faithfully,

(Dr. Geeta Jaywani)

True Copy

ANNEXURE P-7

FORTIS HOSPITAL

INSTITUTE OF BLOOD DISORDERS AND BONE MARROW TRANSPLANT

Highlights:

- Team of eight doctors including haematologists, haemato-oncologists and stem cell transplant team.
- Already completed over 120 bone marrow transplants in just one year.
- 22-bedded transplant unit
- Outcomes driven by global protocols (10 percent mortality).
- One of the largest centres for multiple sclerosis, sickle cell and aplastic anaemia treatment
- Global standard of infection control practises
- One of the few centres performing matched unrelated donor transplant for thalassemia
- 40 percent long term outcome data for haploidentical transplant
- Already treating patients from 18 different countries - first Indian hospital to do a BMT transplant from Trinidad & Tobago

The Department of Haematology, Paediatric Haemoto-oncology & Bone Marrow Transplantation at Fortis Memorial Research Institute (FMRI) provides broad-ranging, integrated and patient-centric services for the diagnosis and management of all kinds of blood disorders in adults and children, including cancers of the blood.

Backed by an extensive team of experienced haematologists, the Department strives to become the most sought after center for the diagnosis & management of benign and malignant haematological disorders, laboratory haematological services and blood transfusion services.

Experts at the Department are experienced at treating different conditions including:

- Anaemia
- Sickle Cell Disease
- Immune Deficiency Disorders
- Thalassemia Major
- Autoimmune Disease
- Acute Myeloid Leukemia
- Acute Lymphoblastic Leukemia

- Multiple Myeloma
- Clotting Disorders
- Bleeding Disorders
- Paediatric Solid Tumours (Ewings / Osteosarcomas / Neuroblastomas)

The Department always remains at the forefront of existing methods and advancements in haematology services, making for a dynamic, efficient and self-reliant center with a wide array of specialisms.

Our highly qualified multidisciplinary team is comprised of adult haematologists and paediatric haemato-oncologists that offer treatment of and research into complex blood disorders. Moreover, our constant quest to advance our knowledge and methods puts us at the extreme edge of what is possible, making for a dynamic team offering services of superlative clinical quality.

We are proud of our highest standards of patient care, which lies at the heart of all our activities. Our supportive services are second to none, making our steadfast and highly specialized center a place of contentment for patients suffering from any kind of blood disorder.

Hematopoietic Stem Cell Transplant (HSCT Treatment) For Multiple Sclerosis At Fortis Memorial Research Institute (FMRI), Gurgaon India

Hematopoietic Stem Cell Transplant (HSCT Treatment) for Multiple Sclerosis at at Fortis Memorial Research Institute (FMRI), Gurgaon India

How does the HSCT Treatment Work?

HSCT Medical Team At Fortis Memorial Research Hospital, India

Fortis MEMORIAL
RESEARCH INSTITUTE
GURUGRAM

True copy

Annexure 8/8

ANNEXURE P-9

MILAAP

Your support could save Baby Radhika from lifelong blood transfusions

My name is Ashutosh Jha and I am raising funds for my 3 yrs old Daughter Radhika Jha who is suffering from Thalassemia Major and is undergoing treatment (Haplo Identical Bone Marrow Transplant) at Dharamshila Hospital, New Delhi (Reg. ID: C94242). The treatment is costing us **Rs. 25-30 Lakhs** and we need funds to continue the treatment and save her life.

She has a 1 year old brother Shivansh and he is also suffering from same. Currently both require blood transfusion twice in a month. As the time passes BMT success rate goes down. This is start of their life, later they would require blood more frequently. As we will delay in treatment, possible risk will be also increase day by day. So we want it to be done early. So we have to do BMT for both baby as soon as possible. To avoid lifelong blood transfusion and their side effect.

We didn't found any 10/10 unrelated Bone Marrow Match, we tried our best but highest match we found with 8/10. No any doctor agreed to do BMT with that match. So we have only option to perform Haplo-identical BMT in Private Hospital. We have been explained that ***Haplo-identical BMT is***

currently not established as standard of care for Thalassemia Major, and same is carried out in institutionally approved clinical study.

All Govt. Hospitals including AIIMS does transplant only with 10/10 sibling as a donor.

She is feeling much better now Currently Radhika is discharged on day 28 after total 35 days of stay in Hospital. On 04th April 2018 transplant is done. She is feeling much better now. She started gaining lost weight during treatment and counts are also much improved. On day 40 HB count is 10.5 Platelet at 1,23,000 and TLC at 4.61.

Big salute to doctors Dr. Suparo Chakrowarti and Dr. Sarita Rani Jaiswal, nursing staffs and House keeping staffs who provided support 24x7 during our stay in hospital.

I am working in Amdocs Pune, our corporate insurance not giving cover for this as it comes under Genetic disease. So to arrange fund I have asked for donations from relatives, friends and colleagues.

All these done within our estimated estimate. Total expense till now ~26 Lakh and estimates for upcoming followups ~2.5 Lakhs. We had received ~18 Lakh from donations and rest from my savings and loans from friends and relatives. Now no more donation needed.

We are grateful for your help!

To know more about Haplo-identical BMT and hospital see below URL http://www.dhrc.in/haploidentical-bmt.html

You can Send your blessings to Radhika on my personal mail forevercoolashu@gmail.com.

You can follow below facebook page to stay updated about Radhika.

ANNEXURE P/10

94

No. Z. 28020/17/2018-NHM-1
Government of India
Ministry of Health & Family Welfare
(NHM-I Division)

Nirman Bhawan, New Delhi
Dated the 11th March, 2018

To,
Mr. Amit Kumar Agrawal
72, Kaveri Apartment, Bandar Bagicha
Dak Bangla Road, Patna, Bihar – 800 001.

Subject: Furnishing of information under RTI Act, 2005.

Sir,

1. I am directed to refer to your RTI application dated 29.01.2018 requesting information under the RTI Act, 2005. In so far as NHM-I, Section under Ministry of Health & Family Welfare is concerned, it is stated that no approval/recognition has been given by this Division to the HEPLO STEM CELL transplant for Thallassemia affected children.
2. The Appellate Authority in the matter is Ms. Limatual Yaden, Appellate Authority and Director, Ministry of Health & Family Welfare, Room No. 210-D, Nirman Bhawan, New Delhi.

Yours faithfully,
Sd/-
(Aruna Bahl Sen)
Under Secretary & CPIO (NHM-I)

Copy of : Section Officer, RTI Cell, MoHFW, Nirman Bhawan (for information only).

(True copy)

ANNEXURE P-11

GOVERNMENT OF RAJASTHAN

DIRECTORATE, MEDICAL AND HEALTH SERVICES
RAJASTHAN, JAIPUR

FILE NO. .....F/62/RTI2005/2018.560 Dated 14.05.2018

Shri Prem Praksh S/o Kishanchand
Evergreen House, 1-B, 14,
Vikas Nagar, Bundi 323001,
Rajasthan

Sub. Under the Right to Information Act, 2005 to supply the information that is seeking by Shri Prakashchand S/o Shri Kishanchand

Ref. Concerned to the subject regarding supply of information through by letter issued by the Public Information Officer and Director (Public Health) Rajasthan, Jaipur letter vide no. E/Cir/RTI-05/F-211/2018/575 dated 30.04.2018

That as on the basis of aforesaid subjected request for supply of information is given to you with the following sequence.

Question	Reply
1. Whether the Bone Marrow Transplant and Halo stem cell transplant has been recognized by your department to the affected the children with Thalisemia?	The department of the directorate of the Health was not given permission for the Bone Marrow Transplant and Halo stem cell transplant to the children affected the with Thalisemia
2. The complaint that is sent to the department (copy enclosed) dated 19/20-02.2018 through by registered postal order that is acknowledged by your department what type of action taken from?	The copy of the enclosed photocopy was not received in respect to your complaint sent by you to the department.

Sd/-
Dy. Director (Medica Superintendent)
Medical and Health services

97

Rajasthan, Jaipur

Dated 1405.2018

Ref. Letter No. MS/F62/RTI-05/2018/560

1. Director of Public Information Officer Rajasthan, Jaipur through letter ref. No. E/Cir/RTI-2005/F-211/2018/575 dated 30.04.2018

2. Enclosed Letter

Sd/-
Dy. Director (Medica Superintendent)
Medical and Health services
Rajasthan, Jaipur

ANNEXURE P-12

Dear Mr. Amit Agrawal,

28th April, 2018

Greetings from Soni Manipal Hospital!

In response to your RTI Application field before Government of Rajasthan seeking certain clarifications pertaining to the concerned subject matter, we write to respond to you as detailed below. Our responses are queries as enlisted by you

Q.1 Is Haploidentical Bone Marrow Transplant (BMT) approved by Government?

Answer- Haploidentical Transplants are a sub-type of BMT and since in BMT there is no involvement of organs being taken out (from donors) and (putting-) implanting in a patient BMT doesn't come under "Transplant of Human Organs Act", (THOA) 1994. The above Act to the best of our knowledge has been amended twice by the Govt. of India in 2011 and 2014 and BMT doesn't come under the scope of this Act, which means that it doesn't need any approval from Govt. agencies.

& The THOA Act and its amendments are attached as annexure no.1 for your reference.

Since, BMT deals with hematopoietic stem cells, question that if that also needs approvals becomes pertinent? The Indian Council of Medical Research (ICMR) in 2017 laid down the guidelines. The relevant part clearly states that these guidelines "Do not apply to use of hematopoietic stem cells for treatment of various haematological, immunological and metabolic disorders since these have already been established as a standard of medical care".

& The ICMR guidelines are attached as annexure no.2 for your reference

There are some 8 BMT centres in India, who are performing these high end transplants and Manipal Hospital, Jaipur is one of them. Kindly see annexure no. 6 showing the training and experience of our BMT Physician for your reference.

Haploidentical BMT means transplant from a donor which is 50% matched or less than 100% matched and this is done when we don't have a 100% matched donor available either in the family or outside in the bone marrow donor registries. It is done only when family makes a written consent after understanding the pros and cons of this procedure. As you might be aware that Bone Marrow Transplant is the only cure available for these unfortunate kids.

In almost every disease where a BMT is indicated as a curative option, the world takes 50% HLA matched BMT as an option when we don't have a 100% HLA matched donor available India as a country doesn't have big bone marrow donor registries and the chance of finding a 100% matched donor in a sibling are just 25% (means most kids wouldn't have a 100% HLA matched donor in family), so as a country we started performing these 50% HLA matched BMT in an attempt to provide this viable chance of cure to all our kids. See table no. 1 for results of Haploidentical BMT in thalassemia major kids.

& Published experience of Thalassemia Haploidentical Transplants (International and national) across the globe as annexure no.3 and 5 for your reference.

& NHS guidelines and European BMT guidelines establishing thalassemia haplo transplant as a standard clinical option are attached as annexure no.4 for your reference

Q.2 What's the success rates of Thai Haploidentical BMT at Manipal Hospital, Jaipur?

Answer – Before we delve in to success rates, let's examine the international scenario, to begin with.

The first paper by Prof. Lucarelli produced a success rate around 70% in 2011. Then came paper from Thailand and U.S.A where they showed a success rate around 90% which we discuss during our routine haploidentical BMT counselling. Based on these papers and international guidelines world, including India started doing these 50% matched BMT in thalassemia major kids. The outcome of majority of Indian BMT centres for haploidentical transplants is around 60-65%. Kindly see the table as annexure no. 5 for your reference.

For better understanding of transplant data, one has to see that BMT success depends on how good (low risk) or poorly (high risk) a thalassemia child has been treated or kept by the family before transplant. Even when we do a 100% HLA matched transplant, the success rates depend on if patient was in low risk or high risk category before BMT. The survival in low risk children is around 85% and in high risk children it's around 50-55% across the globe. I am attaching that paper which shows that high risk thalassemia kids undergoing 100% matched BMT have a success rates around 50-55% (see annexure no.5 for your reference).

Now let's address the question of data from Manipal Hospital, Jaipur. The success rate in any BMT is assessed in terms of "Transplant related Mortality" (death in less than 100 days of BMT, and is attributed to BMT) and overall survival.

We have done 26 Thalassemia Haploidentical BMT at Manipal Hospital, Jaipur over the last 2½ years. Out of 26 Thalassemia Haploidentical BMTs, we lost 8 kids due to BMT complications in less than 100 days post BMT (TRM), which makes mortality rates around 30% and BMT success rates around 70%. Since, we have lost three more kids after 100 days of BMT (these three kids ideally don't come under TRM), that makes total deaths to 11 out of 26 BMTs and this brings overall thalassemia transplant success rates to around 60% in Haploidentical Transplants, at Manipal Hospital Jaipur.

In our cohort of thalassemic Haploidentical BMT patients, 10 patients out of 26 were low risk and 16 were high risk kids. The success rate at our centre in low risk kids is 80% (we lost only 2 children out of 10) and is around 50% (we lost 6 out of 16 in first 100 days and then three more late deaths makes it total 9 deaths out of 16) in high risk patients.

Our data clearly shows that success rates of haploidentical BMT (50% matched donor) in Thalassemia major kids at Manipal Hospital, Jaipur is at par with international standards of 100% and 50% matched transplants.

& Table showing comparison of data from different Indian institutions doing Thalassemia haploidentical BMT as annexure no.5 for your reference.

& Published experience of 100% matched BMT in thalassemia kids as per their risk category as annexure no.6 for your reference.

Q.3 Total number of transplants for both Cancer and thalassemia kids and their success rates?

Answer- We have done some 44 BMTs in children over the last 30 months at Manipal Hospital, Jaipur. Out of these 44 BMTs, 5 are autologous BMTs (Patient's own stem cells are used after high dose chemotherapy in few cancers) and they all are doing fine, which makes the success rate of autologous BMT to 100% at Manipal Hospital, Jaipur and Rajasthan.

In the remaining 39 allogeneic BMT (where stem cells are taken from a donor within the family, 4 transplants have been done for blood cancers (leukemia) and three out of these 4 are surviving, which makes it 75% overall survival in blood cancer patients.

The results of Thalassemia Haploidentical BMT have been explained to you in response to your question number.2. However, please always remember that success in thalassemia transplant depends on the condition of high or low risk condition of the Kid before BMT.

(Live 6/7)

ANNEXURE P-13

Purified T-depleted, CD34$^+$ peripheral blood and bone marrow cell transplantation from haploidentical mother to child with thalassemia

Pietro Sodani, Antonella Isgrò, Javid Gaziev, Paola Polchi, Katia Paciaroni, M arco Marziali, Maria

Domenica Simone, Andrea Roveda, Aldo Montuoro, Cecilia Alfieri, Gioia De Angelis, Cristiano Gallucci, Buket Erer, Giancarlo Isacchi, Francesco Zinno, Gaspare Adorno, Alessandro Lanti, Lawrence Faulkner, Manuela Testi, Marco Andreani and Guido Lucarelli

Blood 2010 115:1296-1302; doi: https://doi.org/10.1182/blood-2009-05-218982

Abstract

Fetomaternal microchimerism suggests immunological tolerance between mother and fetus. Thus, we performed primary hematopoietic stem cell transplantation from a mismatched mother to thalassemic patient without an human leukocyte antigen–identical donor. Twenty-two patients with thalassemia major were conditioned with 60 mg/kg hydroxyurea and 3 mg/kg azathioprine from day −59 to −11; 30 mg/m^2 fludarabine from day −17 to −11; 14 mg/kg busulfan starting on day −10; and 200 mg/kg cyclophosphamide, 10 mg/kg thiotepa, and 12.5 mg/kg antithymocyte globulin daily from day −5 to −2. Fourteen patients received CD34$^+$-mobilized peripheral blood and bone marrow progenitor cells; 8 patients received marrow graft–selected peripheral blood stem cells CD34$^+$ and bone marrow CD3/CD19-depleted cells. T-cell

dose was adjusted to 2×10^5/kg by fresh marrow cell addback at the time of transplantation. Both groups received cyclosporine for graft-versus-host disease prophylaxis for 2 months after transplantation. Two patients died (cerebral Epstein-Barr virus lymphoma or cytomegalovirus pneumonia), 6 patients reject their grafts, and 14 showed full chimerism with functioning grafts at a median follow-up of 40 months. None of the 14 patients who showed full chimerism developed acute or chronic graft-versus-host disease. These results suggest that maternal haploidentical hematopoietic stem cell transplantation is feasible in patients with thalassemia who lack a matched related donor.

Introduction

The cure for thalassemia involves correcting the genetic defect in a hematopoietic stem cell that results in reduced or absent β-globin synthesis and an excess of α-globin dimers. Intracellular precipitation and accumulation of α-dimers results in ineffective erythropoiesis and hemolytic anemia. Replacing the abnormal thalassemic marrow with allogeneic normal or heterozygous stem cells carrying the functional gene restores appropriate β-globin chain synthesis. Eighty to ninety percent of patients receiving a transplant from a human leukocyte antigen (HLA)–identical sibling or parent become ex-thalassemic after transplantation.[1,2]

In the multiracial populations from the Mediterranean region, Middle East, and Arabian Gulf, the probability of having an HLA-identical related donor is 35% to 40%. Thus, the pool of potential donors must be expanded to cure most children with thalassemia or sickle cell anemia. The outcomes after HLA-matched unrelated donor transplantation for treating thalassemia are

comparable with those after HLA-identical familial transplantation.3 The use of mismatched, unrelated cord blood hematopoietic stem cells is still experimental.

Haploidentical hemopoietic stem cell transplantation has been explored as an option for treating patients with leukemia who lack an HLA-identical sibling or parent donor. However, severe graft-versus-host disease (GVHD) and high graft failure/rejection rates have limited the application of this transplantation modality for patients with thalassemia. Advances that use high doses of T cell–depleted peripheral blood stem cells (PBSCs) and intensive pretransplantation conditioning regimens have helped to overcome these limitations.4 Grafts containing megadoses of enriched $CD34^+$ progenitor cells can be achieved by combining bone marrow with granulocyte colony-stimulating factor–mobilized PBSCs. Thereafter, T cells can be removed by positive selection for CD34. Limiting the numbers of $CD3^+$ cells in the graft might allow retention of rapid engraftment kinetics provided by the mobilized PBSCs while reducing the risk of extensive GVHD. In this pilot study, we used a similar approach involving megadose haploidentical positively selected $CD34^+$marrow and peripheral hematopoietic stem cell transplantation to treat patients with thalassemia who lack an HLA-identical familial or unrelated marrow donor. Positive selection of $CD34^+$ stem cells results in an approximately 3- to 4-log reduction of $CD3^+$ cells, which reduces the risk of GVHD but increases the risk of graft failure. Adding a defined dose of $CD3^+$ marrow cells to the cellular suspension at the time of transplantation can help to reduce the graft rejection rate.

In contrast to positive selection of stem cells, marrow graft depleted of $CD3^+$ and $CD19^+$ cells contains significant amounts of monocytes, natural

killer (NK) cells, dendritic cells, precursor T cells, and other cell types that may play important roles in engraftment while accelerating the posttransplantation immune reconstitution. Therefore, in a second prospective phase of this pilot study, we evaluated the use of haploidentical $CD3^+/CD19^+$-depleted marrow graft combined with CD34-selected mobilized PBSCs and $CD3^+$ marrow cells that were added back at the time of infusion. Here, we report the outcomes of 22 children with thalassemia who received transplants from haploidentical donors (20 mothers and 2 brothers).

Methods

During 6 years, 2002 through 2008, 22 patients with thalassemia major received an HLA-haploidentical transplant. Signed informed consent was received before transplantation in accordance with the Declaration of Helsinki, and all procedures were performed according to our center's established protocols. The study protocol was approved by the institutional review board of the Mediterranean Institute of Hematology. The results for 7 patients included in this study have been reported previously and are updated here with longer follow-up.[5,6]

Risk assignment was performed according to published criteria.[7,8] The system categorizes risk on the basis of hepatomegaly, the presence of portal fibrosis on pretransplantation liver biopsies, and the quality of previous chelation (regular: deferoxamine treatment was initiated within 18 months of the first transfusion and administered for 8 to 12 hours as a continuous daily subcutaneous infusion for at least 5 days per week; anything less was considered irregular chelation). The age in months when the patient first received regular chelation was recorded. A chelation index was used to

describe the number of months that each patient did not receive regular chelation as a percentage of the number of months the patient should have received it. With this index, a completely satisfactory chelation history is represented by 0% and a completely unsatisfactory history is represented by 100%.5 Patient characteristics are presented in **Table 1**.

- View inline
- View popup

Table 1

Patient characteristics at transplantation for 22 patients younger than 17 years

Donors

Family members were assessed for HLA compatibility by serological methods or by high-resolution molecular analysis. All donors (20 mothers and 2 brothers) were identical for 1 haplotype and incompatible at 3 loci (HLA-A, -B, -DR) of the other, except for 2 who were mismatched at 2 loci (HLA-A, -B) on the unshared haplotype. One brother was mismatched for noninherited maternal antigens. The stem cell dose was achieved with a median of 3 leukaphereses (range, 1-5). Twenty-one donors had β-thalassemia minor, and one had sickle cell trait.

A total of 10 age- and sex-matched healthy donors were included as control subjects. The control subjects provided bone marrow aspirates, all of which were deemed normal. None of the control subjects had acute infections or were receiving medication at the time of the study.

Graft processing and transplantation procedures

All donors received recombinant human granulocyte colony-stimulating factor 15 μg/kg/d in 2 daily subcutaneous boluses to mobilize PBSCs. $CD34^+$ cells from leukaphereses and bone marrow harvests were selected by the use of the CliniMACS one-step procedure (Miltenyi Biotec) for 14 donors. A 2-step selection ($CD34^+$selection leukapheresis followed by negative selection by the use of anti-CD3 and anti-CD19 monoclonal antibodies [mAbs]) of bone marrow cells was used for 8 donors. We attempted to suppress erythropoiesis by intensive hypertransfusion and chelation. Between day −59 and day −11 before the transplantation, 40 mg/kg deferoxamine was continuously infused through a central venous catheter each 24 hours. Red cells were transfused every 3 days to maintain the hemoglobin level between 140 and 150 g/L (14 and 15 g/dL). During this time interval hydroxyurea 60 mg/kg daily and azathioprine 3 mg/kg daily were administered to eradicate marrow, and growth factors, granulocyte colony-stimulating factor and erythropoietin, were given twice weekly to maintain stem cell proliferation in the face of hypertransfusion, thereby facilitating the effect of the hydroxyurea. Fludarabine was administered at a dosage of 30 $mg/m^2/d$ from day −17 through day −13. Starting on day −10, 14 doses of busulfan 1 mg/kg were administered orally 3 times daily during the course of 4 days (total dose 14 mg/kg during the course of 4 days) in the first 17 patients, and a corresponding dose of busulfan was given intravenously in the following 5 patients, followed by intravenous cyclophosphamide 50 mg/kg daily for each of the next 4 days (total dose, 200 mg/kg), and 10 mg/kg thiotepa and 12.5 mg/kg antithymocyte globulin.

All patients received cyclosporine for GVHD prophylaxis for the first 2 months after transplantation. Antifungal prophylaxis included liposomal

amphotericin B (1 mg/kg daily) from day +8. Cytomegalovirus (CMV) prophylaxis consisted of 5 mg/kg acyclovir 3 times daily through day +60.

Tests for chimerism

Fluorescence in situ hybridization.

When the host and donor were sex mismatched, fluorescence in situ hybridization was performed on peripheral blood and bone marrow to detect marrow engraftment.[9]

DNA extraction.

High molecular weight DNA was extracted from peripheral blood or bone marrow by the use of a commercial DNA blood mini kit, in accordance with the manufacturer's instructions (QIAGEN).

Polymerase chain reaction.

To evaluate chimerism, 4 different minisatellite loci (33.6, SE33, APOB, and D1S80) were amplified by polymerase chain reaction (PCR). The PCR-amplified products were resolved on precast 10% nondenaturing polyacrylamide gel (NOVEX), and the gels were silver-stained. Mixed chimerism was estimated semiquantitatively by the comparison of recipient and donor band intensities with those of known standards.[10]

Graft content

Eight patients received T cell–depleted peripheral blood progenitor cells ($CD34^+$immunoselection) and $CD3^+$- and $CD19^+$-depleted bone marrow stem cells. Median infused cell doses per kilogram of recipient body weight were

$CD34^+$: 15.2 × 10^6(range, 8.2-26 × 10^6); $CD3^+$ T cells: 1.8 × 10^5 and 0.27 × 10^6/kg CD19.

Fourteen patients received $CD34^+$-mobilized peripheral and bone marrow progenitor cells. Positive selection was performed by use of the CliniMACS procedure. The $CD34^+$ grafts contained a median of 14.2 × 10^6/kg $CD34^+$ cells (range, 5.4-39 × 10^6/kg), 2 × 10^5/kg $CD3^+$ cells, and 0.19 × 10^6/kg $CD19^+$. No side effects were associated with graft infusion.

Flow cytometric analysis of peripheral blood mononuclear cells.

For whole blood phenotype analysis, 500 μL of blood was lysed with 10 mL of Ortho-mune Lysing Reagent (Ortho Diagnostic Systems Inc) at room temperature, washed, and labeled with a cocktail of 4 mAbs for 30 minutes at 4°C. Anti–CD3-fluorescein isothiocyanate, anti–CD4-allophycocyanin, anti–CD8-peridinin chlorophyll protein, and anti–CD19-PE were purchased from BD Biosciences.

The NK phenotype of PBMCs was assessed by immunofluorescence and flow cytometry by the use of fluorescein isothiocyanate–conjugated anti-CD3 and PE-conjugated anti-CD56 mAbs (BD Biosciences). After staining, cells were washed once in phosphate-buffered saline containing 2% fetal bovine serum and analyzed on a FACSCalibur cytofluorometer (BD Biosciences) with the use of CellQuest software. Absolute lymphocyte counts were calculated by standard hemocytometry. To determine marker expression on $CD4^+$ and $CD8^+$ cells, total lymphocytes were first identified and gated by forward and side scatter, and then these cells were gated for CD4 or CD8 expression.

Statistical analysis

Estimates of overall survival and event-free survival were calculated by the Kaplan-Meier method.11 Rejection and nonrejection mortality were calculated as cumulative incidences.12 Rejection, recurrence of thalassemia, and death were recorded as events when estimating event-free survival. Rejection was defined as the development of complete marrow aplasia or recurrence of thalassemia (a return to the pretransplantation pattern of globin-chain synthesis).

Results

All patients showed donor chimerism by day 14 after HSCT. Granulocyte counts greater than 500 mL occurred after a median time of 13 days (range, 11-17 days). Six patients rejected their grafts; surviving with thalassemia, 3 patients showed early mixed chimerism (MC), which became persistent when observed, respectively, at 14, 38, and 42 months after the transplantation. In 14 cases the transplantation was successful with complete allogeneic reconstitution. In patients who showed allogeneic reconstitution, median time for granulocyte recovery was 13 days (range, 11-17 days), whereas median time for a self-sustained platelet recovery was 12 days (range, 9-17 days). There were 2 patients who died from transplantation-related causes: one of these patients died on day +114 of Epstein-Barr virus (EBV) cerebral lymphoma, and one died on day +92 from CMV pneumonia. In 6 cases, donor marrow was rejected with complete autologous reconstitution and return to pretransplantation clinical status. In 2 of these patients, rejection occurred after transient engraftment of donor cells. MC has already been described.13 MC was classified, according to the proportion of residual host cells present in the recipient, into MC level 1 (residual host cells < 10%), MC

level 2 (residual host cells between 10% and 25%), and MC level 3 (residual host cells > 25%). Three patients experienced a status of MC early after bone marrow transplantation, which became persistent when observed, respectively, at 14, 38, and 42 months after the transplantation. To define the condition of MC better, we analyzed the proportion of donor engraftment in different lymphoid subsets at different times after bone marrow transplantation (BMT). **Figures 1⇓** through **3** report the MC condition in each of 3 patients.

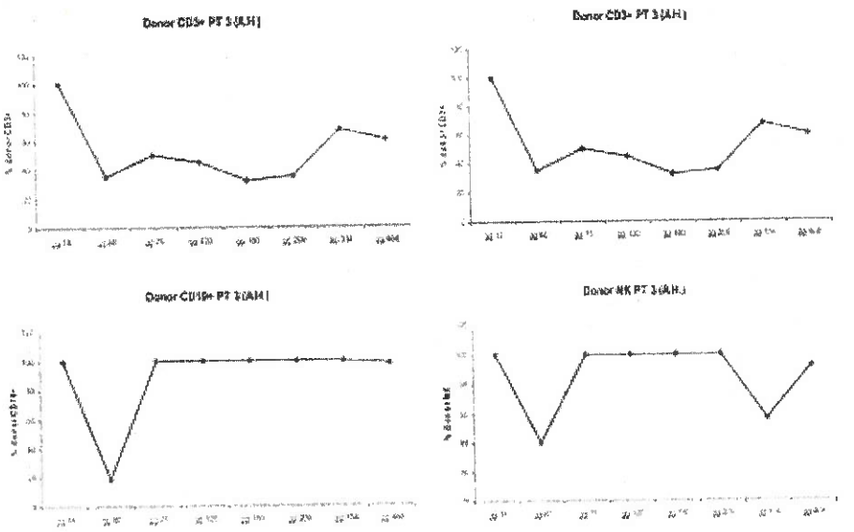

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Figure 1

Kaplan-Meier probabilities of survival, thalassemia-free survival, and cumulative incidence of rejection and nonrelapse mortality in 22 thalassemic patients younger than 17 years of age.

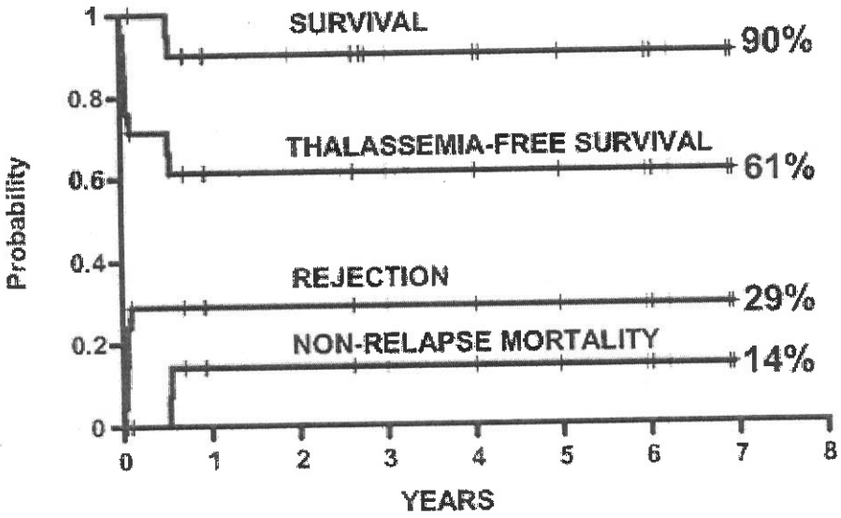

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Figure 2

Proportion of donor engraftment in different lymphoid subsets at different times after BMT (patient 1).

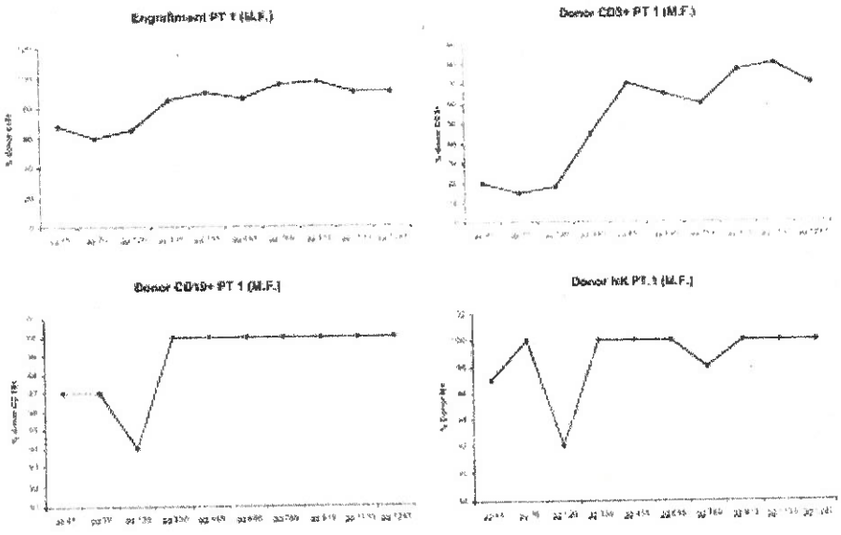

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Figure 3

Proportion of donor engraftment in different lymphoid subsets at different times after BMT (patient 2).

Fourteen patients developed functioning grafts at a median follow-up of 40 months. The 14 cured children are not transfusion dependent any longer, with hemoglobin levels ranging from 10.3 g/dL to 13.8 g/dL, and have an optimal quality of life.

Since the first transplantation performed by our group in Pesaro on February 15, 1989, more than 1000 thalassemic patients have successfully undergone transplantation. Their life is normal, that is, they are socially active, most have regained fertility, more and more are having children. A group working in Pescara has recently published their data.**14** None of the children with full as well persistent MC developed GVHD (**Figure 4**).

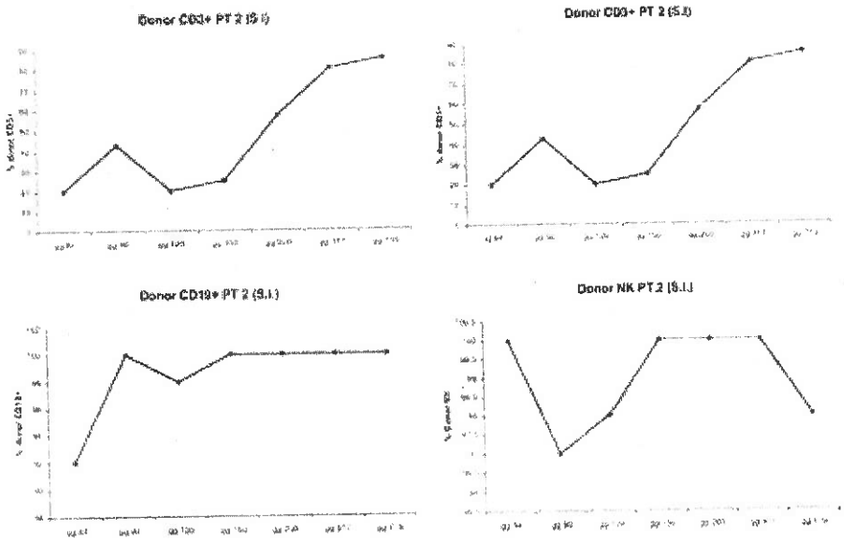

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Figure 4

Proportion of donor engraftment in different lymphoid subsets at different times after BMT (patient 3).

On day +119, 1 patient developed varicella zoster meningoencephalitis (documented by PCR of cerebrospinal fluid) that responded to a combination

of acyclovir and foscarnet. The 2 drugs were combined because the patient had been receiving acyclovir prophylaxis. On day +135, this patient also received a donor lymphocyte infusion (5×10^4 $CD3^+$ donor cells/kg) to boost antivaricella zoster T cells. The donor, who had a history of varicella zoster, had been administered a dose of varicella zoster vaccine 1 week before peripheral lymphocyte collection. The patient recovered with no neurological sequelae or abnormalities on magnetic resonance imaging.

Fifteen patients demonstrated CMV infection without disease that resolved with preemptive gancyclovir treatment. Three patients had EBV reactivation with a high viral load that resolved after treatment with retuximab.

Immunological reconstitution

Delayed immune reconstitution after transplantation may be associated with a variety of functional and immunophenotypic abnormalities at bone marrow level as the result of augmented local production of inflammatory cytokines, increased T-cell activation, or intrinsic hematopoietic and stromal cell abnormalities. At day +20, 6 of 14 patients had significantly lower $CD4^+$ T-cell counts than did the control subjects (1.9 ± 1.4% vs 47.5 ± 6%, respectively). This reduction was mainly in the $CD45RA^+CD62L^+$ (naive phenotype) subset (1.3 ± 2% in patients vs 52 ± 12% in control patients). A significant decrease in peripheral $CD45RA^+CD31^+$ Th cells (thymic-naive Th cells) was observed (0.5 ± 0.3% in patients vs 37 ± 10% in controls), whereas $CD8^+$ T-cell numbers were similar in patients and control patients (24.2 ± 33.7% vs 20 ± 7%). NK cells were among the first lymphocytes to repopulate peripheral blood, and up to 70% of these cells were $CD56^{bright}$, whereas $CD56^{dim}CD16^+$ NK cells were reduced.

On day +60, increases in the percentages of $CD4^+$ T cells, naive $CD4^+$ cells, and thymic-naive Th cells were observed (3 ± 1.2%, 2.9 ± 2.1%, and 2.7 ± 1%, respectively). $CD8^+$ T cells were also increased (35 ± 27.5%). In addition, patients showed a significant increase in $CD4^+$-cell activation markers (CD95, HLA-DR, and CCR5) that paralleled an increase in $CD56^{dim}CD16^+$ NK cells (potent cytotoxic effector cells), especially in the patients with full engraftment (47 ± 20% vs 28 ± 31% in MC).

The stromal layers cultured on chamber slides were positive for CD68, vimentin, and CD14 but negative for S100 and CD34, indicating cells of macrophage/monocyte lineage.**21** In the patients with delayed immunohematological reconstitution, the majority (80%) of these cells appeared moderately large, rounded, and with abundant cytoplasm on light microscopy. In contrast, approximately 90% of stromal cells from control subjects were irregular or spindle shaped with branching cytoplasmic processes (fibroblast-like). Spontaneous stromal cell production of interleukin-7 (IL-7) was lower in patients than in control patients (0.3 ± 0.1 pg/mL vs 0.8 ± 0.1 pg/mL, respectively; $P = .02$).

Discussion

Hematopoietic stem cell transplantation offers the only chance of cure for patients with thalassemia. Haploidentical transplantation may extend this possibility to the 50% to 60% of the patients who lack a suitably matched familial donor or an HLA-identical unrelated donor.

The presence of fetal cells in maternal blood and of maternal cells in fetal blood (fetomaternal microchimerism) suggests that immunological tolerance

may exist between mother and offspring.15,16 Van Rood et al demonstrated a lower rate of acute GVHD in sibling transplants mismatched for noninherited maternal antigens than in transplants mismatched for noninherited paternal antigens.17 We have reported the results of BMT in children with acute leukemia in relapse who are resistant to chemotherapy in which their haploidentical mother was used as the donor of nonmanipulated bone marrow.18

The combination of a megadose of purified $CD34^+$ cells and a highly immunomyeloablative conditioning regimen is crucial for overcoming the barrier of residual antidonor cytotoxic T-lymphocyte precursors in T cell–depleted mismatched transplants.19 The immune regulatory role of $CD34^+$ cells is supported by the observation that cells within the $CD34^+$ population are endowed with veto activity20; early myeloid $CD33^+$ cells may also have this potential.

The infusion of 2×10^5 cell/kg bone marrow mononuclear cells freshly obtained from the bone marrow of the donor requires cyclosporine prophylaxis for GVHD during the first 2 months after transplantation. However, the addition of bone-marrow mononuclear cells (including NK cells, mesenchymal stem cells, T cells) to a T cell–depleted allograft may help promote engraftment and control GVHD.

Haploidentical transplantation is associated with major posttransplantation immune deficiency resulting in significant morbidity and mortality from infection. Delayed immune reconstitution after transplantation may be associated with a variety of functional and immunophenotypic abnormalities at BM level because of augmented local production of inflammatory cytokines, increased T-cell activation, or intrinsic hematopoietic and stromal

cell abnormalities. At 20 days after transplantation, a significant decrease in total lymphocyte counts and depletion of $CD4^+$ T cells expressing predominantly the $CD45RA^+CD62L^+$ phenotype were observed. Also, in the $CD4^+CD45RA^+CD31^+$ T-cell subset in vivo and in vitro, hematolymphopoiesis occurs in association with the complex network of cell types found in the stroma, including nonhematopoietic (fibroblasts, adipocytes, and endothelial cells) and hematopoietic cells (macrophages and T cells). Progenitor cell growth and differentiation depend on their interaction with stromal cells. The prevalence of macrophage-like cells in long-term bone marrow culture, rather than the typical "fibroblast-like" cells, suggests an altered composition of the bone-marrow stroma, possibly linked to an underlying inflammatory process within the bone marrow microenvironment.

A central function of stromal cells is IL-7 production. Recent evidence shows that IL-7 acts as a master regulator of T-cell homeostasis, expanding both the naive and memory T-cell populations. Compared with control patients, thalassemia patients exhibited altered stromal cytokine production at 20 days after transplantation, characterized by decreased IL-7 levels. We can hypothesize that the delayed immunoreconstitution of the T-cell compartment may be initially the result of altered generation of new T cells arising from hematopoietic progenitor cells with the interaction of impaired stromal cell function. NK $CD56^{+bright}$ cells develop more rapidly than other lymphocytes, but $CD3^-CD16^+$ NK cells (with cytotoxic potential) require more prolonged exposure to maturation factor (IL-2) in the bone marrow. Interestingly, we observed greater percentages of NK $CD56^{+bright}$ cells 20 days after transplantation in patients with full engraftment, suggesting a role for donor

NK cells in improved engraftment and in prevention of rejection by an attack of the host lymphohematopoietic cells.

After 60 days after transplantation, a significant decrease in total lymphocyte counts and depletion of $CD4^+$ T cells expressing predominantly the $CD45RA^+CD62L^+$phenotype were observed. In addition, the $CD4^+CD45RA^+CD31^+$ T-cell subset was significantly reduced in our cohort, suggesting a thymus involvement in these patients. Indeed, it is possible that the T-cell defect in thalassemia patients may occur at multiple levels, including egress from thymus.

NK $CD56+^{bright}$ cells develop more rapidly than other lymphocytes, but $CD3^-CD16^+$NK cells (with cytotoxic potential) require more prolonged exposure to maturation factor (IL-2) in the bone marrow. The greater percentages of $CD3^-CD16^+$ in MC patients may have a possible role on control of host cell escape and in maintainer the chimerism condition.

NK cells ($CD56^+$) developed more rapidly than other lymphocytes, but $CD56^{dim}CD16^+$ NK cells were increased at 60 days after transplantation, particularly in patients with full engraftment, suggesting a role for donor NK cells in bone marrow engraftment.**21**

The prevalence of macrophage-like cells in long-term bone-marrow culture as opposed to typical "fibroblast-like" cells suggests that the composition of the marrow stromal was altered, possibly the result of an underlying inflammatory process within the bone marrow microenvironment. Stromal cells produce IL-7, which acts as a growth and antiapoptotic factor for B- and T-cell precursors. This IL-7 production may be critical for the development of the new immune system from uncommitted progenitors infused with the graft. Stromal IL-7 production was decreased in transplant recipients, suggesting an important

role for bone marrow accessory cells in immunohematological reconstitution after transplantation. We hypothesize that the recovery of the T-cell compartment resulted from deregulated production of new T cells from hematopoietic stem cells under the influence of the stromal microenvironment. The results of this study suggest that it may be possible to boost engraftment and immune recovery via the administration of specific cytokines (ie, IL-2 + IL-7) and/or mesenchymal stem cells. One patient died on day +114 of EBV cerebral lymphoma. The patient had low levels of $CD8^+$ at the time of infection. No association between the number of $CD19^+$ cells infused and occurrence of EBV reactivation was found. Despite the high incidence of CMV reactivation, only one patient died of CMV pneumonia. In conclusion, the transplantation protocol described herein appears to be well tolerated and effective for eradicating the hematopoietic system in patients with thalassemia.

(from copy)

Minimum Standards for Hematopoietic Stem Cell Transplantation (HSCT) Units for Blood Diseases

Adapted for India from ASCO/ASH Recommended Criteria for the Performance of Hematopoietic Stem Cell Transplantation (HSCT)

The following criteria are **necessary at a minimum** for the safe and successful performance of the procedure:

1. **Patient Volume**

   a. A sufficient number of patients must be treated each year to allow the development of a designated transplant unit with an experienced, full-time clinical and nursing team.

   b. This would require, in general, that the center performs a minimum of ten transplants per year.

   c. Sufficient transplants must be performed to never have the unit empty.

   d. If both allogeneic and autologous transplants are performed, at least 10 of each should be performed annually to allow sufficient experience in the technical aspects of both procedures to remain current.

   e. Criteria for matched unrelated donors (MUD)/ Haplo identical donors and cord blood transplants – The centre must have completed at least 20 allogeneic transplants.

   f. For new units, compliance with these volume goals should be reached within **3 years** of operation.

2. **Facilities**

   a. There must be a designated transplant unit with two or more designated transplant beds. This could be part of a facility for treating immunosuppressed patients that also manages patients with leukemia or similar disorders.

   b. The equipment and experience necessary for handling the marrow outside the body needs to be in place. This includes at least the facilities and a protocol for cryopreservation of autologous hematopoietic stem cells, and management of ABO blood group incompatible allogeneic transplants if both autologous and allogeneic transplants are performed.

   c. If allogeneic HSCT **is** performed, the transplant unit must demonstrate access to a certified histocompatibility laboratory for the necessary tissue typing.

   d. The transplant unit must have facilities in place and a policy for the required isolation to effectively manage these patients. This should include a plan for air-

handling (e.g. positive pressure, filtered air, or laminar air flow rooms) as well as monitoring of its quality. Support of trained housekeeping staff for maintaining the facility is also critical.

e. Twenty-four hour, high quality support from laboratory, blood bank and radiology needs to be available. This must include the 24-hour availability of red cells, platelets, and other blood components (with facilities available either in house or outsourced for irradiation of cellular blood products).

f. In most circumstances, a radiotherapy unit with the ability to perform and monitor total body radiotherapy should be available if total-body irradiation (TBI) based conditioning is practiced.

g. ICU and dialysis facilities should be available for both adults and children in the institution.

3. Personnel

a. Transplant Physicians

Although the management of patients undergoing HSCT is in many ways not much different from those patients being treated for acute leukemia, physicians who actually perform HSCT should have documentable experience with the procedure. (Defined in the next section)

If both autologous and allogeneic transplants are being performed, the treating physicians should have documentable experience with both types of procedures.

b. Consulting Physicians

Access to a broad range of subspecialty consultations in both medical and surgical specialties such as intensivist, ID specialist etc., required to cope with complications often associated with HSCT need to be immediately available.

c. Nursing Team

This is the most important single aspect of a successful HSCT unit. There need to be nurses committed to this program full-time. There should be a high ratio of nurses to patients with the nurse-to-patient ratio of not more than **1:2** on average. The number of patients transplanted must be sufficient to develop and maintain a full-time nursing team.

d. There must be a commitment from the institution to have full-time HSCT coordinators and adequate support from social work and other services needed.

e. Appropriate microbiology laboratory facilities should be available 24 hours.

f. Resident staff, if DM/DNB training facilities are available at the institute, or 24 hour medical cover of transplant unit by Medical Officer (MBBS or MD) / Consultant should be available.

4. Treatment Outcome

a. A sufficient number of patients in each disease group undergoing treatment at the center is necessary to be able to compare the results with those published from very experienced centers.

b. An occasional patient from any disease group being transplanted should be discouraged.

c. The unit must maintain a registry of all transplants performed, and compare outcomes with results in other centers.

d. There should be a policy in place for identifying deficiencies in results, and for analyzing causes and implementing changes aimed at improving results.

5. Data Reporting

HSCT is a rapidly evolving therapeutic modality. Physicians performing this procedure should report their data to available registries (e.g. Indian Stem Cell Transplant Registry, International Blood and Marrow Transplant Registry) and when appropriate, publish important observations in the medical literature.

Suitable infrastructure for maintenance of treatment records and data reporting must be made available at the institution.

6. Transplant In-Charge Requirements (ref ASBMT guidelines)

Physicians performing peripheral blood, cord blood, and bone marrow transplantations must be licensed to practice medicine and should be board certified or eligible and have the requisite training and experience in hematology, medical oncology, immunology, and/or pediatric hematology/oncology.

Qualifications

a. DM/DNB Clinical Hematology with specific training in stem cell transplantation

b. DM/DNB Medical Oncology with specific training in stem cell transplantation

c. DM/FNB Pediatric Hematology / Oncology with specific training in stem cell transplantation

d. Candidates with MD / DNB (Internal Medicine /Pediatrics) should undergo at least 2 years of training in a recognized department of Hematology with at least one year of training in SCT.

e. Equivalent qualifications from USA / UK / Australia with at least one year of training in HSCT.

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ANNEXURE-B/15

National Guidelines for Stem Cell Research

Indian Council of Medical Research
Department of Health Research
&
Department of Biotechnology
2013

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National Guidelines for Stem Cell Research

Indian Council of Medical Research
Department of Health Research
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2013

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सत्यमेव जयते
Government of India

Foreword

The field of stem cell research is still young. Successful culture and characterization of human embryonic stem cells was achieved just over a decade ago. Since then, some advances have been made towards understanding the basic biology of stemness and their differentiation into different cell lineages, but harnessing of their promised potential to usher in the era of regenerative medicine is still a long way to go. Several clinical trials have been carried out using autologous or allogenic CD34+ve hematopoietic stem cells or mesenchymal stem cells (MSCs) in a variety of clinical indications but most of these have been Phase I or early Phase II trials. There is no conclusive proof of safety or therapeutic efficacy of stem cells in any condition yet. Unfortunately, some clinicians have started exploiting hapless patients by offering unproven stem cell treatments prematurely. Such fraudulent practices need to be stopped urgently, while ensuring that scientifically designed and responsible research on stem cells is not hindered. In 2007, the Indian Council of Medical Research and the Department of Biotechnology jointly released Guidelines for Stem Cell Research and Therapy, which now need to be revised to reflect new scientific and clinical findings that have significantly changed the scope of stem cell research and possible translation.

The present guidelines have retained the earlier classification of stem cell research into three categories, namely Permitted, Restricted and Prohibited categories; an additional layer of oversight, besides the Institutional Ethics Committee (IEC), in the form of Institutional Committee for Stem Cell Research (IC-SCR) and National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) has been introduced. This mechanism of additional review has been accepted by the scientific community in the country and the required NAC-SCRT has become operational. The role and functioning of these committees is being streamlined.

Since 2007 there have been several new developments in the field of stem cell research that significantly change the landscape. This includes the development of induced Pluripotent Stem (iPS) cells by introduction of a limited number of genes into adult somatic cells, paving the way for the generation of histocompatible or patient-specific pluripotent stem cells. Also, progress has been made in growing stem cells without xenogeneic feeder cells; and in well-defined media free from foetal calf serum. However, significant challenges remain with respect to characterizing the cell product for therapy for its purity, safety and potency in an expeditious and cost-effective manner. Updated guidelines are therefore critical to incorporate these advances and to harmonize them with the internationally revised guidelines. Towards this end, the Indian Council of Medical Research (Department of Health Research) and the Department of Biotechnology have conducted a series of public consultations in different parts of the country to elicit the views of various stake holders including scientists, physicians, members of civil society, patient groups, media and industry. The Drafting Committee has taken cognizance of these deliberations and also held in-depth discussions with various expert groups over an extended period, to prepare these revised guidelines.

One major recommendation of the Committee has been to omit the word Therapy from the title of the Guidelines. This has been done to emphasize the fact that stem cells are still not a part of standard of care; hence there can be no guidelines for therapy until efficacy is proven. These guidelines are intended to cover only stem cell research, both basic and translational, and not therapy. It has been made clear in these Guidelines that any stem cell use in patients, other than that for hematopoietic stem cell reconstitution for approved indications, is investigational at present. ***Accordingly, any stem cell use in patients must only be done within the purview of an approved and monitored clinical trial with the intent to advance science and medicine, and not offering it as therapy. In accordance with this stringent definition, every use of stem cells in patients outside an approved clinical trial shall be considered as malpractice.*** It is hoped that this clear definition will serve to curb the malpractice of stem cell "therapy" being offered as a new tool for curing untreatable diseases.

The Indian Council of Medical Research (Department of Health Research) and the Department of Biotechnology gratefully acknowledge the contribution of Prof. Shyam Agarwal in strategizing, conceptualising and finalizing the National Guidelines for Stem Cell Research.

Dr. K. VijayRaghavan
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Indian Council of Medical Research (ICMR), Department of Health Research (DHR) and Department of Biotechnology (DBT) gratefully acknowledge the contribution made by the members of the Drafting Committee for updating Guidelines for Stem Cell Research, keeping in view the opinions of various stakeholders and also the recent developments in the field of Stem Cell Research.

ICMR and DBT also acknowledge the participation of scientists, physicians, members of civil society, patient groups, media and industry during public consultations on Guidelines for Stem Cell Research & Therapy (2007) conducted in different parts of the country to have consensus on the document.

The Division of Basic Medical Sciences, Indian Council of Medical Research organized a series of meetings of Drafting Committee for these Guidelines. The valuable contributions of (Late) Dr. S. S. Agarwal, Chairman and Dr. A. N. Bhisey, Co-chairman of drafting committee in steering and active discussion by members during these meetings are highly appreciated. Special thanks are due to the three member sub-committee of NAC-SCRT headed by Prof. N. K. Mehra for their contribution in giving shape to this document. We gratefully appreciate Dr. Alok Srivastava, Chairman and all members of the NAC-SCRT for finalization of National Guidelines for Stem Cell Research (2013).

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New Delhi
December, 2013

Dr. Vijay Kumar
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Abbreviations

CDSCO	-	Central Drugs Standard Control Organization
CTRI	-	Clinical Trial Registry India
DBT	-	Department of Biotechnology
DCGI	-	Drugs Controller General of India
DNA	-	Deoxy-ribonucleic Acid
DST	-	Department of Science and Technology
ECM	-	Extra Cellular Matrix
GCP	-	Good Clinical Practices
GLP	-	Good Laboratory Practices
GMP	-	Good Manufacturing Practices
GOI	-	Government of India
GTP	-	Good Tissue Practices
EGC	-	Embryonic Germ Cells
ESC	-	Embryonic Stem Cells
iPSC	-	Induced Pluripotent Stem Cells
HLA	-	Human Leukocyte Antigens
HMSC	-	Health Minister's Screening Committee
HSC	-	Hematopoietic Stem Cell
HSCT	-	Haematopoietic Stem Cell Transplantation
IAEC	-	Institutional Animal Ethics Committee
IC-SCR	-	Institutional Committee for Stem Cell Research
ICM	-	Inner Cell Mass
ICMR	-	Indian Council of Medical Research
IEC	-	Institutional Ethics Committee
IND	-	Investigational New Drug
IPR	-	Intellectual Property Rights
IVF	-	In-vitro Fertilization
MOU	-	Memorandum of Understanding
MSC	-	Mesenchymal Stem Cells
MTA	-	Material Transfer Agreement
MTP	-	Medical Termination of Pregnancy
NAC-SCRT	-	National Apex Committee for Stem Cell Research and Therapy
NBE	-	New Biological Entity
PSC	-	Pluripotent Stem Cell
SCNT	-	Somatic Cell Nuclear Transfer
SOP	-	Standard Operating Procedures
SSCs	-	Somatic Stem Cells
TOP	-	Termination of Pregnancy

Guidelines for Stem Cell Research

1.0 Preamble

Use of stem cells in regenerative medicine holds promise for improving human health by restoring the function of cells and organs damaged due to degeneration or injury. Stem cell biology has potential application in several areas of biomedical research that includes drug development, toxicity testing, developmental biology, disease modelling, tissue engineering etc. Like many innovations, stem cell research also involves scientific, ethical and social issues. Apart from challenges of using appropriate stem cells for a particular condition, there are important issues related to the use of embryos for creating human embryonic stem (hES) cell lines. As these may lead to commoditization of human tissues and cells, there is inherent risk of exploitation of individuals particularly those belonging to the underprivileged groups, and challenges related to the contentious issue of human germ-line engineering and reproductive cloning.

Premature use of stem cells for therapy before obtaining adequate data on their safety and efficacy has created an unprecedented problem related to therapeutic profligacy with vulnerable patients being exploited. The potential danger of tumorigenicity of stem cells considering their capacity for unlimited proliferation, possibility of genomic changes arising during *in-vitro* manipulations, and limitations related to immunological tissue incompatibility between individuals are all causes for concern. Of equal importance is the assurance of safety and rights of those donating stem cells of all types for basic and clinical research. Safeguards must be in place to protect subjects receiving stem cells through enrolment in clinical trials. Societal concerns regarding compensation for research related injuries and adverse effects are all also issues that need to be addressed.

As with any new scientific development having the potential for improving human health, research in this field must be regulated with special attention to these issues. The guiding philosophy should be to promote scientific and ethical stem cell research while preventing premature commercialization and potential exploitation of vulnerable patients.

The revised version of the National Guidelines for Stem Cell Research 2013 takes into consideration the above mentioned issues. It also takes note of the fact that

pluripotent stem cells of different kinds have entered clinical trials and hence appropriate guidelines are required for their use.

2.0 Aim and Scope

These Guidelines apply to all stakeholders including individual researchers, organizations, sponsors, oversight/regulatory committees and any others associated with both basic and clinical research on all types of human stem cells and their derivatives. These guidelines do not apply to research using non-human stem cells or tissues. Further, they do not regulate the use of hematopoietic stem cells for treatment of various haematological, immunological and metabolic disorders which has already been established as a standard of medical care.

The guidelines reiterate that the general principles of biomedical research involving human participants shall also be applicable to all human stem cell research.

2.1 The Guidelines specify unique provisions of stem cells, because of their potential for unlimited proliferation, differentiation to cells of the germ layers, regeneration of tissues, and their involvement in pre-implantation stages of human development. The guidelines therefore include:

2.1.1. Procurement of gametes, embryos and somatic cells for derivation and propagation of pluripotent and multipotent stem cell lines, their banking and distribution.

2.1.2. Regulated differentiation into desired progenitor cells and their characterization,

2.1.3. Use of human stem cells and other progenitors derived from them, or their products for basic and clinical research.

The guidelines have been laid down to ensure that research with human stem cells is conducted in a responsible and ethical manner and complies with all regulatory requirements pertaining to biomedical research in general and of stem cell research in particular.

It is important to recognize that this is a rapidly evolving field hence; the recommendations may change over time. It is the responsibility of the researcher and the Institutional Review Committees to understand the principles of these guidelines and keep abreast with the existing regulations in the country.

3.0 General Principles

Research on human subjects involving cells and tissues derived from human embryos and foetuses must safeguard human rights, dignity, and fundamental freedom. This includes processes related to obtaining human tissues and cells for research, diagnosis and therapy. The fundamental tenets of beneficence, non-malfeasance, justice and autonomy should be adhered to in all research involving human subjects. To achieve these objectives, all research involving the use of stem cells must be guided by the general principles laid down in the *"Ethical Guidelines for Biomedical Research on Human Participants"* published in 2006 by the Indian Council of Medical Research (ICMR) and specific principles related to stem cells as detailed in Section 4 of these guidelines must be followed.

The general principles to be followed are given below:

- Principle of essentiality
- Principles of voluntariness, informed consent and community agreement
- Principle of non-exploitation
- Principle of privacy and confidentiality
- Principle of precaution and risk minimization
- Principle of professional competence
- Principle of accountability and transparency
- Principle of maximization of public interest and distributive justice
- Principle of institutional arrangements
- Principle of public domain
- Principle of totality of responsibility
- Principle of compliance

The details of the above may be seen in the parent document (http://www.icmr.nic.in/ethical_guidelines.pdf)

4.0 Ethical Considerations Determining Specific Principles Related to Stem Cell Research

Stem cells are unique in many ways. The two basic characteristics of stem pluripotent cells are their capacity for self-renewal and multi lineage differentiation. They may survive indefinitely and differentiate unpredictably when introduced into

the human host. They may also give rise to tumours such as teratomas. Some of the major concerns that are specific to their collection, processing, storage and use, particularly of the human ES cells for translational research are listed below:

4.1 **Health and Safety of Donors**: Prior to procurement of stem cells for research, it is mandatory to obtain informed consent from the donor. The donor must be informed about the need for screening of transmittable diseases (about which the donor may or may not be aware of) and possible risks involved in donation particularly during major invasive procedures such as ovum or bone marrow donation, under local or general anaesthesia. The donor shall also be informed that cell lines may be generated from the donated material and that these may be banked and shared with other scientific groups. The cell lines may also undergo genetic manipulation, and have the potential for commercialization. In the latter event however, the Intellectual Property Rights (IPR) will not vest with the donor. Also, while confidentiality and privacy are sacrosanct, provision must be made for traceability in a contingency situation. The donor should be made aware that he/she may be contacted in future for specific requirements.

Special care needs to be taken when cells are obtained from embryos and foetuses. Also, donation of gametes and embryos raise special ethical and moral concerns. It is necessary to ensure that the donors are not exploited and commoditized.

4.2 **Manufacture and Quality Assurance of Stem Cell Products**: It is recognised that human adult tissues also have an inherent population of stem cells. In order to obtain these cells in sufficient numbers, some degree of processing, enrichment and/or *in vitro* expansion may be required. Further, manipulations may be needed to enhance their utility. One of the challenges in testing the potency of stem cells is the lack of suitable animal models. Innovative surrogate assays are needed for the purpose.

4.2.1 In case of human ES or iPS cells, targeted differentiation may be required to generate appropriate cells of interest and to separate them from undifferentiated cells. For individualized preparation of iPS cells, abbreviated tests of safety and efficacy are needed to provide timely release of the therapeutic product.

4.2.2 Cell culture techniques require stringent controls to avoid contamination and batch to batch variation. In case autologous or histocompatible iPS cells are used, the cell product should be processed individually for each patient.

4.2.3 Therapeutic cell products should be prepared as in compliance with the GLP/GMP/GTP guidelines and other laboratory conditions depending on the purpose of each use.

4.2.4 All reagents and media used in the process should be of 'clinical grade', intended to be administered to humans.

4.2.5 Stringent characterization of the product with reference to its identity, purity and safety as well as genomic stability, tumorigenicity and potency is essential before its release for human use.

4.2.6 Appropriate quality control and assurances should be in place.

4.3 **Design of Clinical Trials**: Clinical trials using stem cells need to be planned carefully, with follow-up periods suitable for the subject being evaluated, and should also incorporate appropriate end points. It is essential that stakeholders involved in the clinical trials related to stem cells are fully conversant with the current regulations in the field. It is important to ensure that no unproven stem cell therapy is offered outside of the well-controlled clinical trials.

4.4 **Specific Requirements:** Keeping the above considerations in mind, it is emphasized that besides general principles of biomedical research, specific principles need to be evolved to regulate stem cell research, particularly in relation to its translational role. This document is an effort in this direction, to ensure that progress in the field for potential benefit to mankind does not get stymied. To achieve this objective three fundamental principles as under must be followed:

4.4.1 An extra layer of oversight by those who are knowledgeable about the special issues related to stem cells

4.4.2 Periodic evaluation of advances in the field by expert groups and appropriate modification of regulations as and when deemed necessary

4.4.3 Categorizing of stem cell research into three areas viz. permitted, restricted and prohibited, according to the expected risk and level of supervision required for each category. For details, please refer to Section 6 of this document.

4.5 **Intellectual Property Rights and Social Responsibility:** Research on stem cells/ lines and their applications may have considerable commercial value. Appropriate IPR protection may be considered on the merits of each case. If the IPR is commercially exploited, a proportion of the benefits shall be returned to the community, which

has directly or indirectly contributed to the product. "Community" includes all potential beneficiaries such as patient and research groups.

5.0 Classification of Stem Cells

Based on the cell type/tissue of origin, stem cells are classified into *Somatic Stem Cells (SSCs)*, and *Embryonic Stem Cells (ESCs)*. SSCs have limited differentiation capacity and may be multipotent or unipotent. ESCs on the other hand are pluripotent and this characteristic can also be generated by reprogramming of somatic cells, giving rise to induced Pluripotent Stem Cells (iPSCs). The regulatory requirements for research on stem cells depend on their origin and potency.

5.1 ***Somatic Stem Cells (SSCs)*** are a resident, self-renewable population of cells which are present in virtually all organs/tissues of the body. They are essentially undifferentiated, resident in differentiated tissues and are committed to the lineage of that organ. They may, however, have limited plasticity.

5.1.1. SSCs obtained from different sources viz., the foetus, umbilical cord, placenta, infant, child or adult; and from different organs/tissues, may vary in their proliferative and differentiation potential.

5.1.2. The SSCs in bone marrow, skin and gastrointestinal tract continuously divide and differentiate throughout life, but in other organs they remain dormant until they are required for repair and replacement.

5.1.3. SSCs are present in relatively low numbers in most tissues, and may therefore need to be enriched and expanded prior to use. Prolonged cell culture/expansion carries the risk of contamination with microorganisms and potential genomic alterations which should be avoided. Further, cells, culture media and other ingredients, particularly those of animal origin, may carry the risk of introducing xenogeneic pathogens and inducing immune reactivity.

5.1.4. Research on SSCs largely falls under the permitted category and can be carried out with prior approval of the Institutional Committee for Stem Cell research (IC-SCR).

5.2 ***Embryonic Stem Cells (ESCs)*** are derived from pre-implantation embryos. Those derived from embryos before differentiation of trophoectoderm and inner cell mass (i.e. morula stage) are truly totipotent, capable of giving rise to the entire organism and extraembryonic tissues. However, ESCs derived from the inner cell mass (ICM) are pluripotent (not totipotent), having ability to differentiate into derivatives of all three germ layers, viz., ectoderm, mesoderm and endoderm, but not placenta.

5.3 ***Induced Pluripotent Stem Cells*** **(iPSCs),** as the name suggests are pluripotent in nature, quite similar to the ESCs but may not be exactly the same. They are capable of indefinite expansion and differentiation into ectodermal, mesodermal and endodermal cells. The iPS cells can be generated from somatic cells by a variety of genetic and epigenetic methods.

Both ESCs and iPSCs, and their derivatives, can be maintained and expanded as pure populations of undifferentiated cells under appropriate conditions. With appropriate stimuli they can be differentiated into lineage specific progenitor and differentiated cells, e.g., neurons, cardiomyocytes and others. The tumorigenic potential of ESCs and iPSCs is a major safety concern for therapeutic applications.

6.0 Categories of Research on Stem Cells

According to the source of stem cells and nature of experiments, research on human stem cells is categorized into following three areas:

6.1 Permitted Areas of Research

6.1.1 *In vitro* studies on pluripotent stem cell lines viz. ES or iPS cells, or SSCs from foetal or adult tissues, for understanding their basic biology, may be carried out with prior approval of IC-SCR.

6.1.1.1 The ES cell lines used for such research should be established following the ethical guidelines as laid down in this document and should be registered with the NAC-SCRT through IC-SCR.

6.1.1.2 Stem cell lines from sources outside the country should have been established as per the regulatory requirements of the country of origin. These should also meet the National Guidelines as per this document. Documentation/Certification to this effect should be available with the investigator.

6.1.2 *In vivo* studies in experimental animals (other than primates, see Clause 6.2) with established cell lines from any type of human pluripotent stem cells viz., ES, iPS, including differentiated derivatives of these cells, and human SSCs (foetal, neonatal or adult) from any tissue, with prior approval of IC-SCR and IAEC. Such animals shall not be allowed to breed if the stem cells are likely to be incorporated in the gonads. These studies are needed for pre-clinical evaluation of efficacy and safety of human stem cells or their derivatives.

6.1.3 Establishment of new human ES cell lines from spare embryos or iPS cell lines from foetal/adult somatic cells, with prior approval of the IC-SCR, provided appropriate consent is obtained from the donor as per guidelines given in this document (Section 13). Once the ES cell line is established, it shall be registered with NAC-SCRT through IC-SCR with appropriate documentation. Such cell lines to be deposited in an accredited cell bank for use by other investigators. Similarly all iPS cell lines so derived shall be registered with the NAC-SCRT through IC-SCR, if intended for use in clinical research/ trials. Details of their derivation and characterization should be included.

6.1.4 Establishment and licensing of Umbilical Cord Blood stem cell banks falls under purview of the Drug Controller General of India (DCGI). The guidelines notified by CDSCO available at http://cdsco.nic.in/html/GSR%20899.pdf should be followed.

6.1.5 Clinical trials with clinical grade SSCs processed as per National GLP/ GMP / GTP guidelines as applicable (but without major manipulation: see clause 6.1.6.3 below), may be carried out with prior approval of IC-SCR and IEC. Prior approval of DCGI is required if it is intended to seek market authorization for the investigational product. All clinical trials on stem cells shall be registered with Clinical Trial Registry India (CTRI). http://ctri.nic.in/Clinicaltrials/login.php)

6.1.6 **Levels of manipulation**: Before use of stem cells for translation; almost all stem cells, whether autologous or allogeneic, need some degree of in-vitro, or ex-vivo processing before being re-introduced into human body. This carries the risk of contamination and/or alteration in the properties of cells, which may vary according to the degree and type of manipulation. Different degrees of manipulation are defined below:

6.1.6.1 ***Minimal manipulation:*** No intended alteration in cell population or function. This may include separation of mononuclear cells, washing, centrifugation and suspension in acceptable medium and a maximum of overnight storage under appropriate conditions. All laboratory procedures should be carried out under aseptic conditions in a GLP and GMP certified facility.

6.1.6.2 ***Substantial manipulation (or More than minimal manipulation):*** Defined as ex vivo alterations in the cell population (enhancement or depletion of specific subsets), expansion, cryopreservation, or cytokine based activation which is not expected to result in alteration of function. All laboratory processes should be compliant with GLP and GMP certified facilities.

6.1.6.3 ***Major manipulation:*** Genetic and epigenetic modification of stem cells, transient or permanent, which results in alternation of function, is considered to be a major manipulation. This includes transdifferentiation, transduction / transfection by retro / lenti viruses or other gene delivery vehicles to achieve specific selection and expansion of cells of interest. These alterations may also be carried out at transcriptional or translational level. This also includes regulated lineage specific differentiation of human ES and iPS cells into the desired cellular products. Clinical trials using cells which have undergone major manipulation shall require approval of DCGI after obtaining approval from NAC-SCRT through IC-SCR and IEC.

6.1.7 Special care should be taken for cells propagated in culture since they may acquire random genetic alterations. Appropriate screens such as but not limited to cytogenetic and molecular assays should be incorporated as a part of the characterization of cells.

6.1.8 All products intended for administration in humans shall be properly labelled and fulfil the laid down acceptance, release and stability criteria. All procedures shall be well laid down in writing and strictly followed to provide reproducible production of large quantities of well-defined clinical grade cells which meet the desired standards of identity, purity, safety, potency and traceability. The laboratory shall be duly accredited or certified, and file the CMC (Chemistry, Manufacturing and Control) documents for regulatory purposes and necessary approvals.

6.2 Restricted Areas of Research

6.2.1 Creation of a human zygote by IVF, SCNT or any other method with the specific aim of deriving ES cell line for any purpose. This shall require the following:

6.2.1.1 The proposed research cannot be carried out with existing ES cell lines, or those that can be derived from spare embryos;

6.2.1.2 Minimum numbers of embryos/blastocysts required for this research are clearly defined;

6.2.1.3 Research teams involved have appropriate expertise and training in derivation, characterization and culture of ESCs.

6.2.2 Clinical trials using cells derived from the differentiation of human ES or iPS cells, or any stem cell after major manipulation (as defined under Clause 6.1.6.3) shall require approval of DCGI after obtaining approval fromNAC-SCRT through IC-SCR and IEC.

6.2.3 Clinical trials sponsored by multinationals, employing cell products developed outside India, will also need prior approval from DCGI through IC-SCR and IEC.

6.2.4 International collaborative research projects should get clearance from the respective funding agencies as per their established procedure e.g. Health Ministry's Screening Committee (HMSC).

6.2.5 The imports of biological materials for research and development is regulated by Government of India vide their notification (No. L./950/53/97-H1 (Pt.) dated 19th Nov 1997.

6.2.6 Import of 'drugs' (therapeutic products – including cells) requires license from the DCGI as per the regulations.

6.2.7 Research involving introduction of human ES / iPS / SS cells into animals (including primates), *at embryonic or foetal stages of development* for studies on pattern of differentiation and integration of human cells into non-human animal tissues shall conform to the following:

6.2.7.1 If there is a possibility that human stem cells could contribute in a major way to the development of brain or gonads of the recipient animal, the scientific justification for the experiments must be substantiated. Animals derived from these experiments shall not be allowed to breed.

6.2.7.2 Such proposals would need approval of the NAC-SCRT for additional oversight and review through IAEC and IC-SCR.

6.2.8 Studies on chimeras where stem cells from two or more species are mixed at any stage of development viz., embryonic, foetal or postnatal, for studies on pattern of development and differentiation would require prior approval of NAC-SCRT through IC-SCR and IAEC.

6.2.9 Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the human ES/iPS cells were derived is readily ascertainable or could become known to the investigator would also require prior approval of NAC-SCRT through IC-SCR and IEC.

6.3 Prohibited Areas of Research

In the current state of our scientific and technological understanding, research in the following areas is prohibited:

6.3.1 Research related to human germ line gene therapy and reproductive cloning.

6.3.2 *In vitro* culture of intact human embryos, regardless of the method of their derivation, beyond 14 days of fertilization or formation of primitive streak, whichever is earlier.

6.3.3 Clinical trials involving transfer of xenogeneic cells into a human host. Any clinical research on Xenogeneic-Human hybrids is also prohibited.

6.3.4 Research involving implantation of human embryos (generated by any means) into uterus after *in vitro* manipulation, at any stage of development, in humans or primates.

6.3.5 Breeding of animals in which any type of human stem cells have been introduced at any stage of development, and are likely to contribute to gonadal cells.

7.0 Responsibility for Conduct of Stem Cell Research (of Investigator, Institution and Sponsor):

7.1 The investigators and institutions where stem cell research is being conducted bear the ultimate responsibility of ensuring that research activities are in accordance with the national regulations and guidelines. In particular, scientists whose research involves human ES cells should work closely with monitoring/regulatory bodies, demonstrate respect for autonomy and privacy of those who donate gametes, blastocysts, embryos or somatic cells for stem cell research, and be sensitive to public concerns about research that involves human embryos. Those working with human iPS cells shall be particularly careful with the vectors and genes used for induction of stemness against malignant transformation. Sponsors shall also take note of their responsibilities and liabilities under various statutes, regulations and guidelines governing research and development in this field in the country.

7.2 The regulatory bodies shall appreciate that stem cell research is a nascent field. While there have been tremendous advances in understanding the biology of stem cells, there exist several elements of unpredictability in the translation of research in this area. It is of utmost importance that review of research in this field ensures highest degree of scientific rigor and resolution of ethical concerns. Members of the regulatory committee shall regularly update their knowledge with regards to advances in the field.

7.3 Each institution shall maintain a register of its investigators conducting stem cell research and ensure that all registered users are kept up to date with existing guidelines and regulations regarding the use of these cells. It shall also be the responsibility of the institution to ensure that most current standards are applied.

7.4 Each institution shall constitute an IC-SCR as provided in these guidelines and provide adequate support for its functioning. All records pertaining to clinical adult stem cell research must be maintained for a period of at least 5 years and those for ES/iPS cell research for atleast10 years.

7.5 The physician/scientist engaged in stem cell research shall endeavour to avoid any activity that leads to unnecessary hype, or unrealistic expectations in the minds of study subjects or public at large regarding stem cell therapy. The study subject and other responsible family members must be given adequate and unbiased information about the trial protocol, its limitations and potential adverse effects. They must also be informed about the given indication for therapy. The investigator's responsibility is to generate robust scientific evidence through good clinical trials which may then be applied for the benefit of the patients.

7.6 The institutions conducting stem cell research shall establish suitable mechanisms for creating awareness and communicating scientific evidences to the public.

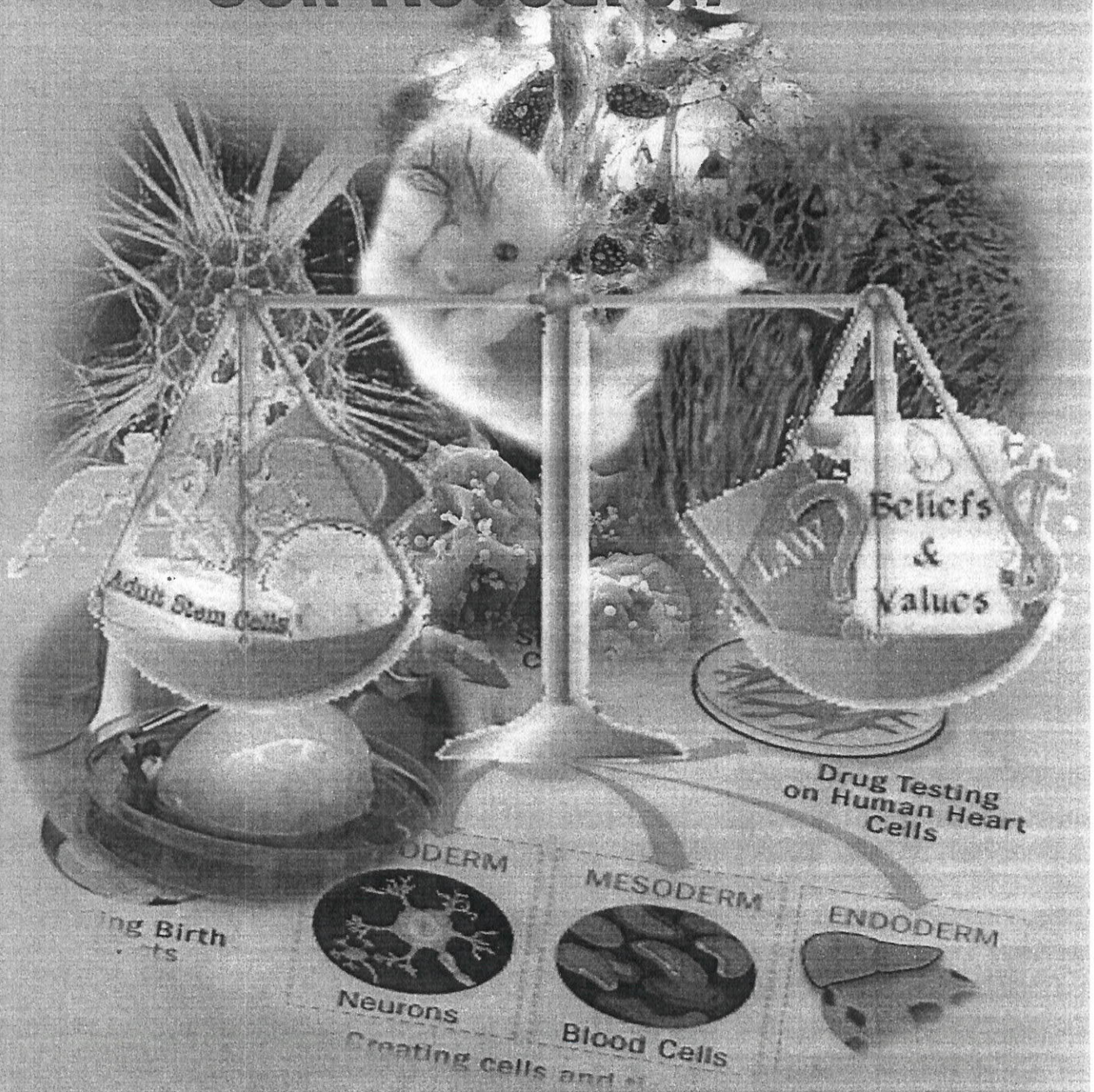
7.7 The basic scientists engaged in human stem cell research shall be vigilant to safeguard rights and dignity of human donors and aborted foetuses from who samples for research have been obtained. The biological material should be treated with utmost respect and care in all experiments. The use of human embryos shall be restricted as much as possible, and shall be resorted to where there are no other alternatives. Also, special care should be taken in introducing human cells in animals, particularly in early developmental stages, which may lead to development of chimeras or incorporation into brain/gonads.

7.8 Several types of research with pluripotent stem cells in the present state of our knowledge and understanding are prohibited (clause 6.3). Guidelines in this document should be strictly complied with, regardless of the arguments of potential benefits that can come from such research.

8.0 Mechanism for Review and Regulatory Oversight of Stem Cell Research

In recent years, the area of stem cell research has undergone rapid developments promising new leads in the treatment of several incurable diseases. Research in the field is associated with unique ethical, legal and social issues that require additional oversight and expertise for efficient scientific and ethical evaluation. Hence, a separate mechanism for review and monitoring is essential both at the institutional as well as the national level. A National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) will monitor and oversee activities at national level and Institutional Committee for Stem Cell Research (IC-SCR) at institutional level. The composition, functions and responsibilities of NAC-SCRT and IC-SCR are given in Annexure I. These oversight committees shall ensure that review, approval and monitoring of all research projects in the field of stem cell research is done rigorously and effectively as per the national guidelines.

National Guidelines for Stem Cell Research



Indian Council of Medical Research
Department of Health Research
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Department of Biotechnology
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National Guidelines for Stem Cell Research

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Government of India

Foreword

The field of stem cell research is still young. Successful culture and characterization of human embryonic stem cells was achieved just over a decade ago. Since then, some advances have been made towards understanding the basic biology of stemness and their differentiation into different cell lineages, but harnessing of their promised potential to usher in the era of regenerative medicine is still a long way to go. Several clinical trials have been carried out using autologous or allogenic CD34+ve hematopoietic stem cells or mesenchymal stem cells (MSCs) in a variety of clinical indications but most of these have been Phase I or early Phase II trials. There is no conclusive proof of safety or therapeutic efficacy of stem cells in any condition yet. Unfortunately, some clinicians have started exploiting hapless patients by offering unproven stem cell treatments prematurely. Such fraudulent practices need to be stopped urgently, while ensuring that scientifically designed and responsible research on stem cells is not hindered. In 2007, the Indian Council of Medical Research and the Department of Biotechnology jointly released Guidelines for Stem Cell Research and Therapy, which now need to be revised to reflect new scientific and clinical findings that have significantly changed the scope of stem cell research and possible translation.

The present guidelines have retained the earlier classification of stem cell research into three categories, namely Permitted, Restricted and Prohibited categories; an additional layer of oversight, besides the Institutional Ethics Committee (IEC), in the form of Institutional Committee for Stem Cell Research (IC-SCR) and National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) has been introduced. This mechanism of additional review has been accepted by the scientific community in the country and the required NAC-SCRT has become operational. The role and functioning of these committees is being streamlined.

Since 2007 there have been several new developments in the field of stem cell research that significantly change the landscape. This includes the development of induced Pluripotent Stem (iPS) cells by introduction of a limited number of genes into adult somatic cells, paving the way for the generation of histocompatible or patient-specific pluripotent stem cells. Also, progress has been made in growing stem cells without xenogeneic feeder cells; and in well-defined media free from foetal calf serum. However, significant challenges remain with respect to characterizing the cell product for therapy for its purity, safety and potency in an expeditious and cost-effective manner. Updated guidelines are therefore critical to incorporate these advances and to harmonize them with the internationally revised guidelines. Towards this end, the Indian Council of Medical Research (Department of Health Research) and the Department of Biotechnology have conducted a series of public consultations in different parts of the country to elicit the views of various stake holders including scientists, physicians, members of civil society, patient groups, media and industry. The Drafting Committee has taken cognizance of these deliberations and also held in-depth discussions with various expert groups over an extended period, to prepare these revised guidelines.

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One major recommendation of the Committee has been to omit the word Therapy from the title of the Guidelines. This has been done to emphasize the fact that stem cells are still not a part of standard of care; hence there can be no guidelines for therapy until efficacy is proven. These guidelines are intended to cover only stem cell research, both basic and translational, and not therapy. It has been made clear in these Guidelines that any stem cell use in patients, other than that for hematopoietic stem cell reconstitution for approved indications, is investigational at present. ***Accordingly, any stem cell use in patients must only be done within the purview of an approved and monitored clinical trial with the intent to advance science and medicine, and not offering it as therapy. In accordance with this stringent definition, every use of stem cells in patients outside an approved clinical trial shall be considered as malpractice.*** It is hoped that this clear definition will serve to curb the malpractice of stem cell "therapy" being offered as a new tool for curing untreatable diseases.

The Indian Council of Medical Research (Department of Health Research) and the Department of Biotechnology gratefully acknowledge the contribution of Prof. Shyam Agarwal in strategizing, conceptualising and finalizing the National Guidelines for Stem Cell Research.

Dr. K. VijayRaghavan
Secretary
Department of Biotechnology

Dr. V. M. Katoch
Secretary
Department of Health Research &
Director General, Indian Council of Medical Research

Acknowledgements

Indian Council of Medical Research (ICMR), Department of Health Research (DHR) and Department of Biotechnology (DBT) gratefully acknowledge the contribution made by the members of the Drafting Committee for updating Guidelines for Stem Cell Research, keeping in view the opinions of various stakeholders and also the recent developments in the field of Stem Cell Research.

ICMR and DBT also acknowledge the participation of scientists, physicians, members of civil society, patient groups, media and industry during public consultations on Guidelines for Stem Cell Research & Therapy (2007) conducted in different parts of the country to have consensus on the document.

The Division of Basic Medical Sciences, Indian Council of Medical Research organized a series of meetings of Drafting Committee for these Guidelines. The valuable contributions of (Late) Dr. S. S. Agarwal, Chairman and Dr. A. N. Bhisey, Co-chairman of drafting committee in steering and active discussion by members during these meetings are highly appreciated. Special thanks are due to the three member sub-committee of NAC-SCRT headed by Prof. N. K. Mehra for their contribution in giving shape to this document. We gratefully appreciate Dr. Alok Srivastava, Chairman and all members of the NAC-SCRT for finalization of National Guidelines for Stem Cell Research (2013).

The patronage of Dr V. M. Katoch, the Secretary, Department of Health Research & Director General, ICMR and Dr. K. VijayRaghavan, Secretary, Department of Biotechnology for their continued support is gratefully acknowledged.

Special appreciations are due to Dr. Geeta Jotwani in co-ordination and compilation of these Guidelines.

New Delhi
December, 2013

Dr. Vijay Kumar
Scientist 'G' and Head
Division of Basic Medical Sciences
Indian Council of Medical Research

Abbreviations

CDSCO	-	Central Drugs Standard Control Organization
CTRI	-	Clinical Trial Registry India
DBT	-	Department of Biotechnology
DCGI	-	Drugs Controller General of India
DNA	-	Deoxy-ribonucleic Acid
DST	-	Department of Science and Technology
ECM	-	Extra Cellular Matrix
GCP	-	Good Clinical Practices
GLP	-	Good Laboratory Practices
GMP	-	Good Manufacturing Practices
GOI	-	Government of India
GTP	-	Good Tissue Practices
EGC	-	Embryonic Germ Cells
ESC	-	Embryonic Stem Cells
iPSC	-	Induced Pluripotent Stem Cells
HLA	-	Human Leukocyte Antigens
HMSC	-	Health Minister's Screening Committee
HSC	-	Hematopoietic Stem Cell
HSCT	-	Haematopoietic Stem Cell Transplantation
IAEC	-	Institutional Animal Ethics Committee
IC-SCR	-	Institutional Committee for Stem Cell Research
ICM	-	Inner Cell Mass
ICMR	-	Indian Council of Medical Research
IEC	-	Institutional Ethics Committee
IND	-	Investigational New Drug
IPR	-	Intellectual Property Rights
IVF	-	In-vitro Fertilization
MOU	-	Memorandum of Understanding
MSC	-	Mesenchymal Stem Cells
MTA	-	Material Transfer Agreement
MTP	-	Medical Termination of Pregnancy
NAC-SCRT	-	National Apex Committee for Stem Cell Research and Therapy
NBE	-	New Biological Entity
PSC	-	Pluripotent Stem Cell
SCNT	-	Somatic Cell Nuclear Transfer
SOP	-	Standard Operating Procedures
SSCs	-	Somatic Stem Cells
TOP	-	Termination of Pregnancy

Guidelines for Stem Cell Research

1.0 Preamble

Use of stem cells in regenerative medicine holds promise for improving human health by restoring the function of cells and organs damaged due to degeneration or injury. Stem cell biology has potential application in several areas of biomedical research that includes drug development, toxicity testing, developmental biology, disease modelling, tissue engineering etc. Like many innovations, stem cell research also involves scientific, ethical and social issues. Apart from challenges of using appropriate stem cells for a particular condition, there are important issues related to the use of embryos for creating human embryonic stem (hES) cell lines. As these may lead to commoditization of human tissues and cells, there is inherent risk of exploitation of individuals particularly those belonging to the underprivileged groups, and challenges related to the contentious issue of human germ-line engineering and reproductive cloning.

Premature use of stem cells for therapy before obtaining adequate data on their safety and efficacy has created an unprecedented problem related to therapeutic profligacy with vulnerable patients being exploited. The potential danger of tumorigenicity of stem cells considering their capacity for unlimited proliferation, possibility of genomic changes arising during *in-vitro* manipulations, and limitations related to immunological tissue incompatibility between individuals are all causes for concern. Of equal importance is the assurance of safety and rights of those donating stem cells of all types for basic and clinical research. Safeguards must be in place to protect subjects receiving stem cells through enrolment in clinical trials. Societal concerns regarding compensation for research related injuries and adverse effects are all also issues that need to be addressed.

As with any new scientific development having the potential for improving human health, research in this field must be regulated with special attention to these issues. The guiding philosophy should be to promote scientific and ethical stem cell research while preventing premature commercialization and potential exploitation of vulnerable patients.

The revised version of the National Guidelines for Stem Cell Research 2013 takes into consideration the above mentioned issues. It also takes note of the fact that

pluripotent stem cells of different kinds have entered clinical trials and hence appropriate guidelines are required for their use.

2.0 Aim and Scope

These Guidelines apply to all stakeholders including individual researchers, organizations, sponsors, oversight/regulatory committees and any others associated with both basic and clinical research on all types of human stem cells and their derivatives. These guidelines do not apply to research using non-human stem cells or tissues. Further, they do not regulate the use of hematopoietic stem cells for treatment of various haematological, immunological and metabolic disorders which has already been established as a standard of medical care.

The guidelines reiterate that the general principles of biomedical research involving human participants shall also be applicable to all human stem cell research.

2.1 The Guidelines specify unique provisions of stem cells, because of their potential for unlimited proliferation, differentiation to cells of the germ layers, regeneration of tissues, and their involvement in pre-implantation stages of human development. The guidelines therefore include:

2.1.1. Procurement of gametes, embryos and somatic cells for derivation and propagation of pluripotent and multipotent stem cell lines, their banking and distribution.

2.1.2. Regulated differentiation into desired progenitor cells and their characterization,

2.1.3. Use of human stem cells and other progenitors derived from them, or their products for basic and clinical research.

The guidelines have been laid down to ensure that research with human stem cells is conducted in a responsible and ethical manner and complies with all regulatory requirements pertaining to biomedical research in general and of stem cell research in particular.

It is important to recognize that this is a rapidly evolving field hence; the recommendations may change over time. It is the responsibility of the researcher and the Institutional Review Committees to understand the principles of these guidelines and keep abreast with the existing regulations in the country.

3.0 General Principles

Research on human subjects involving cells and tissues derived from human embryos and foetuses must safeguard human rights, dignity, and fundamental freedom. This includes processes related to obtaining human tissues and cells for research, diagnosis and therapy. The fundamental tenets of beneficence, non-malfeasance, justice and autonomy should be adhered to in all research involving human subjects. To achieve these objectives, all research involving the use of stem cells must be guided by the general principles laid down in the *"Ethical Guidelines for Biomedical Research on Human Participants"* published in 2006 by the Indian Council of Medical Research (ICMR) and specific principles related to stem cells as detailed in Section 4 of these guidelines must be followed.

The general principles to be followed are given below:

- Principle of essentiality
- Principles of voluntariness, informed consent and community agreement
- Principle of non-exploitation
- Principle of privacy and confidentiality
- Principle of precaution and risk minimization
- Principle of professional competence
- Principle of accountability and transparency
- Principle of maximization of public interest and distributive justice
- Principle of institutional arrangements
- Principle of public domain
- Principle of totality of responsibility
- Principle of compliance

The details of the above may be seen in the parent document (http://www.icmr.nic.in/ethical_guidelines.pdf)

4.0 Ethical Considerations Determining Specific Principles Related to Stem Cell Research

Stem cells are unique in many ways. The two basic characteristics of stem pluripotent cells are their capacity for self-renewal and multi lineage differentiation. They may survive indefinitely and differentiate unpredictably when introduced into

the human host. They may also give rise to tumours such as teratomas. Some of the major concerns that are specific to their collection, processing, storage and use, particularly of the human ES cells for translational research are listed below:

4.1 **Health and Safety of Donors**: Prior to procurement of stem cells for research, it is mandatory to obtain informed consent from the donor. The donor must be informed about the need for screening of transmittable diseases (about which the donor may or may not be aware of) and possible risks involved in donation particularly during major invasive procedures such as ovum or bone marrow donation, under local or general anaesthesia. The donor shall also be informed that cell lines may be generated from the donated material and that these may be banked and shared with other scientific groups. The cell lines may also undergo genetic manipulation, and have the potential for commercialization. In the latter event however, the Intellectual Property Rights (IPR) will not vest with the donor. Also, while confidentiality and privacy are sacrosanct, provision must be made for traceability in a contingency situation. The donor should be made aware that he/she may be contacted in future for specific requirements.

Special care needs to be taken when cells are obtained from embryos and foetuses. Also, donation of gametes and embryos raise special ethical and moral concerns. It is necessary to ensure that the donors are not exploited and commoditized.

4.2 **Manufacture and Quality Assurance of Stem Cell Products**: It is recognised that human adult tissues also have an inherent population of stem cells. In order to obtain these cells in sufficient numbers, some degree of processing, enrichment and/or *in vitro* expansion may be required. Further, manipulations may be needed to enhance their utility. One of the challenges in testing the potency of stem cells is the lack of suitable animal models. Innovative surrogate assays are needed for the purpose.

4.2.1 In case of human ES or iPS cells, targeted differentiation may be required to generate appropriate cells of interest and to separate them from undifferentiated cells. For individualized preparation of iPS cells, abbreviated tests of safety and efficacy are needed to provide timely release of the therapeutic product.

4.2.2 Cell culture techniques require stringent controls to avoid contamination and batch to batch variation. In case autologous or histocompatible iPS cells are used, the cell product should be processed individually for each patient.

4.2.3 Therapeutic cell products should be prepared as in compliance with the GLP/GMP/GTP guidelines and other laboratory conditions depending on the purpose of each use.

4.2.4 All reagents and media used in the process should be of 'clinical grade', intended to be administered to humans.

4.2.5 Stringent characterization of the product with reference to its identity, purity and safety as well as genomic stability, tumorigenicity and potency is essential before its release for human use.

4.2.6 Appropriate quality control and assurances should be in place.

4.3 **Design of Clinical Trials**: Clinical trials using stem cells need to be planned carefully, with follow-up periods suitable for the subject being evaluated, and should also incorporate appropriate end points. It is essential that stakeholders involved in the clinical trials related to stem cells are fully conversant with the current regulations in the field. It is important to ensure that no unproven stem cell therapy is offered outside of the well-controlled clinical trials.

4.4 **Specific Requirements:** Keeping the above considerations in mind, it is emphasized that besides general principles of biomedical research, specific principles need to be evolved to regulate stem cell research, particularly in relation to its translational role. This document is an effort in this direction, to ensure that progress in the field for potential benefit to mankind does not get stymied. To achieve this objective three fundamental principles as under must be followed:

4.4.1 An extra layer of oversight by those who are knowledgeable about the special issues related to stem cells

4.4.2 Periodic evaluation of advances in the field by expert groups and appropriate modification of regulations as and when deemed necessary

4.4.3 Categorizing of stem cell research into three areas viz. permitted, restricted and prohibited, according to the expected risk and level of supervision required for each category. For details, please refer to Section 6 of this document.

4.5 **Intellectual Property Rights and Social Responsibility:** Research on stem cells/ lines and their applications may have considerable commercial value. Appropriate IPR protection may be considered on the merits of each case. If the IPR is commercially exploited, a proportion of the benefits shall be returned to the community, which

has directly or indirectly contributed to the product. "Community" includes all potential beneficiaries such as patient and research groups.

5.0 Classification of Stem Cells

Based on the cell type/tissue of origin, stem cells are classified into *Somatic Stem Cells (SSCs)*, and *Embryonic Stem Cells (ESCs)*. SSCs have limited differentiation capacity and may be multipotent or unipotent. ESCs on the other hand are pluripotent and this characteristic can also be generated by reprogramming of somatic cells, giving rise to induced Pluripotent Stem Cells (iPSCs). The regulatory requirements for research on stem cells depend on their origin and potency.

5.1 ***Somatic Stem Cells (SSCs)*** are a resident, self-renewable population of cells which are present in virtually all organs/tissues of the body. They are essentially undifferentiated, resident in differentiated tissues and are committed to the lineage of that organ. They may, however, have limited plasticity.

5.1.1. SSCs obtained from different sources viz., the foetus, umbilical cord, placenta, infant, child or adult; and from different organs/tissues, may vary in their proliferative and differentiation potential.

5.1.2. The SSCs in bone marrow, skin and gastrointestinal tract continuously divide and differentiate throughout life, but in other organs they remain dormant until they are required for repair and replacement.

5.1.3. SSCs are present in relatively low numbers in most tissues, and may therefore need to be enriched and expanded prior to use. Prolonged cell culture/expansion carries the risk of contamination with microorganisms and potential genomic alterations which should be avoided. Further, cells, culture media and other ingredients, particularly those of animal origin, may carry the risk of introducing xenogeneic pathogens and inducing immune reactivity.

5.1.4. Research on SSCs largely falls under the permitted category and can be carried out with prior approval of the Institutional Committee for Stem Cell research (IC-SCR).

5.2 ***Embryonic Stem Cells (ESCs)*** are derived from pre-implantation embryos. Those derived from embryos before differentiation of trophoectoderm and inner cell mass (i.e. morula stage) are truly totipotent, capable of giving rise to the entire organism and extraembryonic tissues. However, ESCs derived from the inner cell mass (ICM) are pluripotent (not totipotent), having ability to differentiate into derivatives of all three germ layers, viz., ectoderm, mesoderm and endoderm, but not placenta.

5.3 ***Induced Pluripotent Stem Cells*** **(iPSCs),** as the name suggests are pluripotent in nature, quite similar to the ESCs but may not be exactly the same. They are capable of indefinite expansion and differentiation into ectodermal, mesodermal and endodermal cells. The iPS cells can be generated from somatic cells by a variety of genetic and epigenetic methods.

Both ESCs and iPSCs, and their derivatives, can be maintained and expanded as pure populations of undifferentiated cells under appropriate conditions. With appropriate stimuli they can be differentiated into lineage specific progenitor and differentiated cells, e.g., neurons, cardiomyocytes and others. The tumorigenic potential of ESCs and iPSCs is a major safety concern for therapeutic applications.

6.0 Categories of Research on Stem Cells

According to the source of stem cells and nature of experiments, research on human stem cells is categorized into following three areas:

6.1 Permitted Areas of Research

6.1.1 *In vitro* studies on pluripotent stem cell lines viz. ES or iPS cells, or SSCs from foetal or adult tissues, for understanding their basic biology, may be carried out with prior approval of IC-SCR.

6.1.1.1 The ES cell lines used for such research should be established following the ethical guidelines as laid down in this document and should be registered with the NAC-SCRT through IC-SCR.

6.1.1.2 Stem cell lines from sources outside the country should have been established as per the regulatory requirements of the country of origin. These should also meet the National Guidelines as per this document. Documentation/Certification to this effect should be available with the investigator.

6.1.2 *In vivo* studies in experimental animals (other than primates, see Clause 6.2) with established cell lines from any type of human pluripotent stem cells viz., ES, iPS, including differentiated derivatives of these cells, and human SSCs (foetal, neonatal or adult) from any tissue, with prior approval of IC-SCR and IAEC. Such animals shall not be allowed to breed if the stem cells are likely to be incorporated in the gonads. These studies are needed for pre-clinical evaluation of efficacy and safety of human stem cells or their derivatives.

6.1.3 Establishment of new human ES cell lines from spare embryos or iPS cell lines from foetal/adult somatic cells, with prior approval of the IC-SCR, provided appropriate consent is obtained from the donor as per guidelines given in this document (Section 13). Once the ES cell line is established, it shall be registered with NAC-SCRT through IC-SCR with appropriate documentation. Such cell lines to be deposited in an accredited cell bank for use by other investigators. Similarly all iPS cell lines so derived shall be registered with the NAC-SCRT through IC-SCR, if intended for use in clinical research/ trials. Details of their derivation and characterization should be included.

6.1.4 Establishment and licensing of Umbilical Cord Blood stem cell banks falls under purview of the Drug Controller General of India (DCGI). The guidelines notified by CDSCO available at http://cdsco.nic.in/html/GSR%20899.pdf should be followed.

6.1.5 Clinical trials with clinical grade SSCs processed as per National GLP/ GMP / GTP guidelines as applicable (but without major manipulation: see clause 6.1.6.3 below), may be carried out with prior approval of IC-SCR and IEC. Prior approval of DCGI is required if it is intended to seek market authorization for the investigational product. All clinical trials on stem cells shall be registered with Clinical Trial Registry India (CTRI). http://ctri.nic.in/Clinicaltrials/login.php)

6.1.6 **Levels of manipulation**: Before use of stem cells for translation; almost all stem cells, whether autologous or allogeneic, need some degree of in-vitro, or ex-vivo processing before being re-introduced into human body. This carries the risk of contamination and/or alteration in the properties of cells, which may vary according to the degree and type of manipulation. Different degrees of manipulation are defined below:

6.1.6.1 ***Minimal manipulation:*** No intended alteration in cell population or function. This may include separation of mononuclear cells, washing, centrifugation and suspension in acceptable medium and a maximum of overnight storage under appropriate conditions. All laboratory procedures should be carried out under aseptic conditions in a GLP and GMP certified facility.

6.1.6.2 ***Substantial manipulation (or More than minimal manipulation):*** Defined as ex vivo alterations in the cell population (enhancement or depletion of specific subsets), expansion, cryopreservation, or cytokine based activation which is not expected to result in alteration of function. All laboratory processes should be compliant with GLP and GMP certified facilities.

6.1.6.3 ***Major manipulation:*** Genetic and epigenetic modification of stem cells, transient or permanent, which results in alternation of function, is considered to be a major manipulation. This includes transdifferentiation, transduction / transfection by retro / lenti viruses or other gene delivery vehicles to achieve specific selection and expansion of cells of interest. These alterations may also be carried out at transcriptional or translational level. This also includes regulated lineage specific differentiation of human ES and iPS cells into the desired cellular products. Clinical trials using cells which have undergone major manipulation shall require approval of DCGI after obtaining approval from NAC-SCRT through IC-SCR and IEC.

6.1.7 Special care should be taken for cells propagated in culture since they may acquire random genetic alterations. Appropriate screens such as but not limited to cytogenetic and molecular assays should be incorporated as a part of the characterization of cells.

6.1.8 All products intended for administration in humans shall be properly labelled and fulfil the laid down acceptance, release and stability criteria. All procedures shall be well laid down in writing and strictly followed to provide reproducible production of large quantities of well-defined clinical grade cells which meet the desired standards of identity, purity, safety, potency and traceability. The laboratory shall be duly accredited or certified, and file the CMC (Chemistry, Manufacturing and Control) documents for regulatory purposes and necessary approvals.

6.2 Restricted Areas of Research

6.2.1 Creation of a human zygote by IVF, SCNT or any other method with the specific aim of deriving ES cell line for any purpose. This shall require the following:

6.2.1.1 The proposed research cannot be carried out with existing ES cell lines, or those that can be derived from spare embryos;

6.2.1.2 Minimum numbers of embryos/blastocysts required for this research are clearly defined;

6.2.1.3 Research teams involved have appropriate expertise and training in derivation, characterization and culture of ESCs.

6.2.2 Clinical trials using cells derived from the differentiation of human ES or iPS cells, or any stem cell after major manipulation (as defined under Clause 6.1.6.3) shall require approval of DCGI after obtaining approval fromNAC-SCRT through IC-SCR and IEC.

6.2.3 Clinical trials sponsored by multinationals, employing cell products developed outside India, will also need prior approval from DCGI through IC-SCR and IEC.

6.2.4 International collaborative research projects should get clearance from the respective funding agencies as per their established procedure e.g. Health Ministry's Screening Committee (HMSC).

6.2.5 The imports of biological materials for research and development is regulated by Government of India vide their notification (No. L./950/53/97-H1 (Pt.) dated 19th Nov 1997.

6.2.6 Import of 'drugs' (therapeutic products – including cells) requires license from the DCGI as per the regulations.

6.2.7 Research involving introduction of human ES / iPS / SS cells into animals (including primates), *at embryonic or foetal stages of development* for studies on pattern of differentiation and integration of human cells into non-human animal tissues shall conform to the following:

6.2.7.1 If there is a possibility that human stem cells could contribute in a major way to the development of brain or gonads of the recipient animal, the scientific justification for the experiments must be substantiated. Animals derived from these experiments shall not be allowed to breed.

6.2.7.2 Such proposals would need approval of the NAC-SCRT for additional oversight and review through IAEC and IC-SCR.

6.2.8 Studies on chimeras where stem cells from two or more species are mixed at any stage of development viz., embryonic, foetal or postnatal, for studies on pattern of development and differentiation would require prior approval of NAC-SCRT through IC-SCR and IAEC.

6.2.9 Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the human ES/iPS cells were derived is readily ascertainable or could become known to the investigator would also require prior approval of NAC-SCRT through IC-SCR and IEC.

6.3 Prohibited Areas of Research

In the current state of our scientific and technological understanding, research in the following areas is prohibited:

6.3.1 Research related to human germ line gene therapy and reproductive cloning.

6.3.2 *In vitro* culture of intact human embryos, regardless of the method of their derivation, beyond 14 days of fertilization or formation of primitive streak, whichever is earlier.

6.3.3 Clinical trials involving transfer of xenogeneic cells into a human host. Any clinical research on Xenogeneic-Human hybrids is also prohibited.

6.3.4 Research involving implantation of human embryos (generated by any means) into uterus after *in vitro* manipulation, at any stage of development, in humans or primates.

6.3.5 Breeding of animals in which any type of human stem cells have been introduced at any stage of development, and are likely to contribute to gonadal cells.

7.0 Responsibility for Conduct of Stem Cell Research (of Investigator, Institution and Sponsor):

7.1 The investigators and institutions where stem cell research is being conducted bear the ultimate responsibility of ensuring that research activities are in accordance with the national regulations and guidelines. In particular, scientists whose research involves human ES cells should work closely with monitoring/regulatory bodies, demonstrate respect for autonomy and privacy of those who donate gametes, blastocysts, embryos or somatic cells for stem cell research, and be sensitive to public concerns about research that involves human embryos. Those working with human iPS cells shall be particularly careful with the vectors and genes used for induction of stemness against malignant transformation. Sponsors shall also take note of their responsibilities and liabilities under various statutes, regulations and guidelines governing research and development in this field in the country.

7.2 The regulatory bodies shall appreciate that stem cell research is a nascent field. While there have been tremendous advances in understanding the biology of stem cells, there exist several elements of unpredictability in the translation of research in this area. It is of utmost importance that review of research in this field ensures highest degree of scientific rigor and resolution of ethical concerns. Members of the regulatory committee shall regularly update their knowledge with regards to advances in the field.

7.3 Each institution shall maintain a register of its investigators conducting stem cell research and ensure that all registered users are kept up to date with existing guidelines and regulations regarding the use of these cells. It shall also be the responsibility of the institution to ensure that most current standards are applied.

7.4 Each institution shall constitute an IC-SCR as provided in these guidelines and provide adequate support for its functioning. All records pertaining to clinical adult stem cell research must be maintained for a period of at least 5 years and those for ES/iPS cell research for atleast10 years.

7.5 The physician/scientist engaged in stem cell research shall endeavour to avoid any activity that leads to unnecessary hype, or unrealistic expectations in the minds of study subjects or public at large regarding stem cell therapy. The study subject and other responsible family members must be given adequate and unbiased information about the trial protocol, its limitations and potential adverse effects. They must also be informed about the given indication for therapy. The investigator's responsibility is to generate robust scientific evidence through good clinical trials which may then be applied for the benefit of the patients.

7.6 The institutions conducting stem cell research shall establish suitable mechanisms for creating awareness and communicating scientific evidences to the public.

7.7 The basic scientists engaged in human stem cell research shall be vigilant to safeguard rights and dignity of human donors and aborted foetuses from who samples for research have been obtained. The biological material should be treated with utmost respect and care in all experiments. The use of human embryos shall be restricted as much as possible, and shall be resorted to where there are no other alternatives. Also, special care should be taken in introducing human cells in animals, particularly in early developmental stages, which may lead to development of chimeras or incorporation into brain/gonads.

7.8 Several types of research with pluripotent stem cells in the present state of our knowledge and understanding are prohibited (clause 6.3). Guidelines in this document should be strictly complied with, regardless of the arguments of potential benefits that can come from such research.

8.0 Mechanism for Review and Regulatory Oversight of Stem Cell Research

In recent years, the area of stem cell research has undergone rapid developments promising new leads in the treatment of several incurable diseases. Research in the field is associated with unique ethical, legal and social issues that require additional oversight and expertise for efficient scientific and ethical evaluation. Hence, a separate mechanism for review and monitoring is essential both at the institutional as well as the national level. A National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) will monitor and oversee activities at national level and Institutional Committee for Stem Cell Research (IC-SCR) at institutional level. The composition, functions and responsibilities of NAC-SCRT and IC-SCR are given in Annexure I. These oversight committees shall ensure that review, approval and monitoring of all research projects in the field of stem cell research is done rigorously and effectively as per the national guidelines.

8.1 All institutes engaged in stem cell research must establish an Institutional Committee for Stem Cell Research (IC-SCR) with necessary expertise in the field as detailed in Annexure I. Alternatively, IC-SCR can be constituted by inducting additional expertise in the existing IEC with the nomenclature as IC-SCR, as per the requirement of these guidelines. The IC-SCR shall discharge all its function as envisaged under these guidelines.

8.2 All institutions and investigators, both public and private, carrying out research on human stem cells should be registered with the NAC-SCRT through IC-SCR.

8.3 Research using human stem cells shall have prior approval of IC-SCR for permitted research and of the NAC-SCRT for restricted research.

8.4 All new human pluripotent stem cell lines, irrespective of the source and methodology used, can be created with prior approval of IC-SCR. However, the use of human embryonic and iPS cells in clinical trials shall have prior approval of the NAC-SCRT. The requirements for taking decisions regarding creation of embryos for the purpose of establishment of stem cell lines are given in details in these guidelines (Clause 6.1.3 and 6.2.1).

8.5 Permission for procurement of human embryonic stem cell lines from abroad or from laboratories/banks in India shall be obtained from IC-SCR. Import must follow the guidelines as per Clause 6.2.5.The investigator shall ensure that imported cell line has been established in accordance with the ethical guidelines of the country of origin which are comparable to Indian guidelines. An appropriate MTA shall be adopted for the purpose.

8.6 All clinical trials with SSCs, other than those with genetic modifications, shall have prior approval of IC-SCR and Institutional Ethics Committee (IEC). Clinical trials using genetically modified SSCs, and ES or iPS cells or derivatives should have prior approval from the NAC-SCRT after obtaining clearance from IC-SCR and IEC.

8.7 All clinical trials using cells that have undergone more than minimal manipulation (Clause 6.1.6.2) shall have to obtained approval from IC-SCR, IEC and DCGI.

8.8 Approval of the Drug Controller General of India (DCGI) is mandatory for stem cell based IND products and application for new indications (cells for therapies are deemed as drugs) with prior clearance from IC-SCR and IEC.

8.9 For market authorization of stem cell derived products, all clinical trials approved by the DCGI shall be registered with the Clinical Trials Registry of India established by ICMR. (http://ctri.nic.in/Clinicaltrials/login.php).

8.10 International collaborations shall have prior approval of respective funding agency as per its procedure or Health Ministry's Screening Committee (HMSC).

9.0 Basic Research

9.1 Derivation and Characterization of Human Pluripotent Stem Cells: General Considerations

9.1.1 All human ESC lines to be used for basic research should be in accordance with the details provided under Clause 6.1.3 of this document. Human iPSC lines to be used for basic research should be registered with IC-SCR.

9.1.2 Derivation of new ES or iPS cell lines from human embryonic or somatic cells respectively, shall adhere to the conditions for gamete, embryo and somatic cell donation as laid down in these guidelines (Section 13), and with prior approval (Clause 6.1.3).

9.2 Basic Stem Cell Biology:

9.2.1 Research on human ESCs and iPSC to increase knowledge about embryo development, infertility treatment causes of miscarriage and birth defects and improving contraception techniques.

9.2.2 Developing methods to detect abnormalities in embryos before implantation.

9.2.3 Developing human disease models (generation of disease specific iPSC) to understand pathophysiological mechanisms at cellular and molecular level.

9.2.4 Developing targeted therapies for genetic and developmental diseases

9.2.5 Developing *in vitro* cell culture systems of stem cells and their progenitors during different stages of cell differentiation for drug discovery and toxicity screening

9.2.6 Advancing current understanding of novel cell-based therapies by studying distribution, differentiation, integration, functioning and survival of implanted cells in experimental animals

9.2.7 Understanding mechanisms responsible for stemness, role of niche, dormancy, recruitment, plasticity and the ability to repair and regenerate

9.2.8 Pre-clinical evaluation of safety and efficacy of cell products developed as new drugs

9.2.8.1 All *in vitro* studies that fall in the permitted category of research (Clause 6.1).

9.2.8.2 Studies carried out on established human stem cell lines registered with the IC-SCR/NAC-SCRT (where no direct contact is required with human subjects to obtain cells), and approved by the scientific review committee may be

exempted from obtaining fresh informed consent by IC-SCR/IEC. Necessary GLP guidelines shall however be followed.

9.2.8.3 Studies performed on cells/tissues directly obtained from human subjects, shall require approval from the IC-SCR and IEC before their initiation.

9.2.8.4 *In vivo* studies on experimental animals (other than primates) that fall in the permitted category should be in accordance with Clause 6.1.2.

9.2.8.5 Studies on chimeras and sub-human primates shall follow Clause 6.2.5.

9.2.9 No *in vitro* studies on pre-implantation human embryos shall be carried out beyond 14 days of fertilization or formation of primitive streak, whichever is earlier. Similarly no *in vitro* manipulated cells shall be implanted in human/animal uterus with the intent of developing a whole organism.

10.0 Translational Research including Clinical Trials Using Stem Cells

This section outlines guidelines for both preclinical studies and clinical trials using stem cells and their derivatives, for repair or regeneration of damaged tissues and organs in situations where application of this mode of therapy has not yet reached an accepted standard of medical care. It involves translational research for generating a safe and effective novel product based on fundamental research that can be taken to the bedside. Besides the scientific, technical and entrepreneurial challenges, it is necessary to address the ethical, social, and regulatory issues associated with this emerging branch of medicine.

In case stem cells are being delivered using implantable or injectable scaffolds, guidelines given in Section 11 should additionally be followed.

10.1 Preclinical

Preclinical studies are essential to establish safety and proof-of-principle, prior to conduct of human clinical trials, as per regulatory requirements for any new biological entity (NBE). These studies involve both *in vitro* and/or experiments using animal model systems. The latter are usually carried out in small animals, with or without immuno-suppression to prevent cell rejection. Only in specific situations and depending on the nature of the study, large animals and/or non-human primates maybe used with prior permission (Clause 10.1.3).

10.1.1 Preclinical studies shall demonstrate safety of the product and the procedure, as well as the proof-of-principle for achieving desired therapeutic effects. The stem cells to be employed in such trials shall be well characterized, similar to the ones to be used in clinical trials, and evaluated both for early and late toxicities including immunogenicity and tumorigenicity.

10.1.2 Diseased human tissues can be permitted for *in vitro* preclinical studies.

10.1.3 ***Approval and Monitoring:*** Preclinical studies shall be approved by IC-SCR and IEC following independent peer review. Approval from IAEC and CPCSEA shall also be obtained for studies involving small and large animals respectively.

10.1.4 ***Study Design:***

10.1.4.1 The stem cells shall be well characterized and the source, dose and route of their administration (local/systemic) shall be clearly defined appropriate to the proposed clinical application. The final product to be administered must be a clinical grade product prepared in a rolling cGMP facility.

10.1.4.2 Besides routine safety studies, distribution of cells, their survival, integration and functional outcome should be evaluated in animal models wherever possible.

10.1.4.3 Large animal models/non-human primates maybe used wherever necessary for example studies involving cardiac physiology; tissue-related inflammatory and immunological injuries and degenerative disorders of weight bearing joints etc. The selected animal model should offer an appropriate context for studying the human disease and conditions of specific interest.

10.1.4.4 For products seeking market authorization, preclinical toxicity studies shall be done in a certified GLP facility.

10.1.4.5 The interaction of stem cells with drugs (including immuno-suppressants wherever relevant) to treat the underlying medical condition shall be tested in animal model/cell culture systems.

10.1.4.6 Study design shall preferably incorporate a plan to analyse potential toxicities arising due to abnormalities acquired during *in vitro* processing

10.1.5 It is recognized that preclinical assays in animal models may not accurately predict the nature of cell behaviour and immune response in humans.

10.2 **Clinical Research/Trial**

Clinical trials using human stem cells should be in compliance with Schedule Y of Drugs and Cosmetics Act and GCP Guidelines of CDSCO (www.cdsco.nic.in) as well as ICMR-Ethical Guidelines for Biomedical Research involving Human Participants (http://www.icmr.nic.in/ethical_guidelines.pdf). Clinical trial protocol shall be formulated as per the format given in Annexure II.

10.2.1 Reagents used for the derivation of human ES or iPS cell lines, or expansion/enrichment of SSCs, for purposes of clinical trials should be of clinical-grade.

10.2.2 ***Trial Subjects:*** Subject selection shall be done according to the predefined inclusion and exclusion criteria, as laid down in the approved clinical research protocol.

10.2.2.1 The patient information sheet and the informed consent form shall specifically address the following:

a. Information regarding the present status of use of stem cells in the given condition, experimental nature of the proposed clinical study and its possible short and long term risks.

b. Information stating irreversibility of the intervention.

c. Information regarding source and characteristics of stem cells and degree of their *ex vivo* manipulation, if any.

d. Information on the established standard of care for a given condition

e. Information on the sample size and duration of study

f. The information sheet and the consent form should be approved by IEC and IC-SCR and the same should be clearly mentioned in these documents.

10.2.3 ***Approval and Monitoring****:*

Approval and monitoring of clinical trials will take into consideration the following factors but not limited to:

10.2.3.1 Source and type of stem cells- somatic, embryonic, iPSC etc.

10.2.3.2 Autologous or allogeneic application

10.2.3.3 Degree of manipulation: minimal, substantial (more than minimal), or major (Clause 6.1.6)

10.2.3.4 Stage of research –*in vitro*, *in vivo*, preclinical or clinical

10.2.3.5 Whether the proposed cell based research is intended for developing a marketable product or an academic institutional research for advancement of knowledge

10.2.4 ***Regulatory Approvals:***

10.2.4.1 All clinical trials using stem cells shall be registered with CTRI http://ctri.nic.in/Clinicaltrials/login.php

10.2.4.2 Clinical trial proposals using minimally manipulated autologous SSCs shall be approved by IC-SCR and IEC.

10.2.4.3 Clinical trials using stem cells with substantial manipulation shall be approved by DCGI after obtaining clearance from IC-SCR and IEC.

10.2.4.4 Clinical trials using allogeneic SSCs (with any degree of manipulation) or autologous SSCs with major manipulation shall be approved by DCGI after obtaining clearance from NAC-SCRT through IC-SCR and IEC.

10.2.4.5 Clinical trials using human ES cells (or their derivatives) shall be approved by DCGI after obtaining clearance from NAC-SCRT through IC-SCR and IEC.

10.2.4.6 Any stem cell based product already approved and marketed outside India (or for concurrent clinical trial in India) will require approval of DCGI through IC-SCR and IEC for pre-license clinical trial.

10.2.4.7 Any clinical trial with a product intended to be licensed and marketed shall have prior approval of DCGI through IC-SCR and IEC.

10.2.5 ***Monitoring of Clinical Trials:***

10.2.5.1 All clinical trials using stem cells involving human subjects shall be monitored by IEC and IC-SCR. All cases of adverse events should be reported to the Data Safety Monitoring Board (DSMB), NAC-SCRT and Funding Agency/Sponsor.

10.2.5.2 Institutes involved in clinical trials using stem cells should constitute separate DSMB for each trial, as appropriate.

10.2.5.3 DSMB shall have the requisite expertise to monitor trials for adverse events and their smooth conduct.

10.2.5.4 Members of the DSMB shall not have any conflict of interest with the study and they should not be associated with IC-SCR/IEC.

10.2.5.5 The IC-SCR and IEC shall ensure that the subjects recruited under clinical trial shall not be charged.

10.2.5.6 The institution and/or sponsor conducting clinical trials shall be responsible for insurance and compensation of the subjects recruited under the trial

10.3 Use of Stem Cells for Therapeutic Purposes

10.3.1 At present, there are no approved indications for stem cell therapy other than the hematopoietic stem cell transplantation (HSCT) for haematological disorders. Accordingly all stem cell therapy other than the above shall be treated as investigational and conducted only in the form of a clinical trial after obtaining necessary regulatory approvals. Use of stem cells for any other purpose outside the domain of clinical trial will be considered unethical and hence is not permissible.

10.3.2 Cells used in clinical trials must be of clinical grade and processed under rolling GTP/GMP standards as considered necessary by the IC-SCR and NAC-SCRT.

10.3.3 The product for transplantation to be used for clinical trial shall be free from animal products and microbial contamination.

10.3.4 Centres carrying out stem cell clinical trials and the agency/ source providing such cells for the trial shall be registered with the NAC-SCRT through IC-SCR.

10.3.5 For International Collaboration, the public funding agency evaluating the study or the Health Ministry's Screening Committee shall ensure that the certification provided by the collaborating country fulfils the requirements as laid down in these guidelines.

10.3.6 For a trial protocol to become an approved therapy, the investigator shall apply to the NAC-SCRT with the data on which such a claim is based and a justification for the same. The NAC-SCRT will then determine, in independent consultation with experts in the field, whether such a claim may be approved.

11.0 Tissue Engineering and Scaffolds in Stem Cell Research

Tissue engineering is an emerging area of biomedical research with the primary goal

of repair/regeneration and restoration of functions of the damaged tissue that fail to heal spontaneously by using cells, growth factors and natural or synthetic scaffolds either alone or in combination. Scaffolds act as the artificial extracellular matrix (ECM), which provide structural support for the cells as they expand and guide their growth in a three-dimensional (3D) space into a specific tissue. To guide the organization, growth, and differentiation of cells in tissue-engineered constructs, the scaffold should be able to provide not only physical support for the cells but also the chemical and biological cues required for function restoration.

An ideal scaffold should possess all the qualities of a native ECM, be biocompatible and should provide a 3D template for the cells to attach and guide their growth. It should have a porous architecture with a high surface area allowing for maximum loading of cells, cell-matrix interaction, tissue in growth and transportation of nutrients and oxygen. It should be mechanically strong to withstand local *in vivo* biological forces but biodegradable. However, the degradation rate should match the rate of regeneration. It should be made of material that can be sterilized without compromising any structural or functional properties. Most importantly, it should allow the cells it supports to perform intended functions. The manufacturing process of scaffold with all the above unique characteristics must be accomplished in a practical, reproducible and scalable manner.

The detailed guidelines for the use of scaffolds in stem cell research are beyond the scope of this document. The investigator is advised to refer to the following:

http://www.astm.org/Standards/F2150.htm

http://www.astm.org/Standards/F2450.htm

http://www.astm.org/Standards/F2027.htm

http://www.astm.org/Standards/F2739.htm

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=28650

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=28653

12.0 Banking of Umbilical Cord Blood and Other Biological Tissues Including Cell Lines:

12.1 Procurement and banking of various biological tissues such as umbilical cord blood, placenta, extracted tooth, adipose tissue and other sources of stem cells with the specific objective of their isolation and/or *ex vivo* expansion is increasingly becoming

a commercial activity. However, care needs to be taken such that there is no exploitation and commoditization of these resources. Each proposal for banking or for academic application of the banked tissue shall be carefully examined by the IC-SCR and IEC from the ethical angle to ensure access, equity and justice. Use of the banked material for commercial purposes may require national consultation regarding intellectual property rights of the donor.

12.2 ***Banking of Umbilical Cord Blood***

12.2.1 Umbilical cord blood is a rich source of CD34+ hematopoietic and mesenchymal (stromal) stem cells. The use of the HSC for treatment of various haematological and immunological disorders is currently well established, particularly where an HLA-matched sibling is not available for HSC donation. To meet this demand, several public (untargeted, non-profit) umbilical cord blood banks have become established all over the world. Such banks are permitted to be established in India, so long as they are licensed by the CDSCO and fulfil the requirements laid down by it. As far as collection and distribution policy and procedure of the umbilical cord blood units for HSCT is concerned, they should follow the standard practices. However, any other use of cord blood stem cells, HSC or MSC is experimental at present and shall be permitted only under conditions of controlled clinical trial by the IC-SCR/IEC or NAC-SCRT through the IC-SCR as required under the provisions of these guidelines.

12.2.2 All cord blood banks must be licensed and monitored by the CDSCO. They should follow the Drugs and Cosmetics (3rd Amendment) Rules, 2011 (Gazette Notification No. GSR 899(E) dated 27/12/2011) for collection, processing, testing, storage, banking, and release of umbilical cord blood (http://cdsco.nic.in/html/GSR%20899.pdf).

There are ethical concerns about the promotional advertisements by private banks offering storage of cord blood for possible future use. Such advertisements are often misleading for the public and lack comprehensive and accurate information to the consumer. It may be mentioned that there is no scientific basis for preservation of cord blood for future self-use and this practice is not recommended. On the other hand, parents should be encouraged for voluntary donation to public cord blood banks for allogeneic transplantation and research purposes. In such cases, ID cards should be issued by the banks, to the donor to enable preferential access/benefits to donor/relatives, in future.

12.2.3 ***Precautions for collection of umbilical cord blood for stem cells***

The following points should specifically be considered while collecting UCB:

12.2.3.1 No harm should occur to the donor neonate.

12.2.3.2 Exact timing of clamping the umbilical cord should be defined in the SOP and recorded in the case file.

12.2.3.3 Parents should be fully informed regarding risks and benefits involved.

12.2.3.4 Voluntary informed consent should be obtained from both parents well before the scheduled delivery date, but in no case at the time of delivery. If there is disagreement between parents, the mother's wish shall prevail.

12.2.3.5 ID card should be issued for voluntary donation to enable preferential access/ benefit in future, in case required for self/ relatives. Such units may also be used for unrelated individuals.

12.2.3.6 Standard operating Procedures for collection, transportation, processing, storage (cryopreservation) and release for clinical use of umbilical cord blood/ cells should be clearly laid down and approved by IC-SCR and IEC.

12.2.3.7 If stem cells are proposed to be processed before use (without major manipulation), detailed protocol for their isolation, expansion, and characterization should be approved by IC-SCR and IEC. If any major manipulation is envisaged, the approval should also be taken from the NAC-SCRT.

12.2.3.8 Period of preservation for self-use later in life should be clearly defined.

12.2.3.9 Detailed SOPs for release of umbilical cord units for clinical use should be in place. This should include follow up plans to monitor the outcome of HSCT for assessing safety and efficacy of cord blood stem cell therapy.

12.3 Banking and Distribution of Human ES/iPS Cell Lines

As human ES/iPS cell research advances, it will be increasingly important for institutions that obtain store and use stem cell lines to have confidence in the value of stored cells. For this purpose, it is necessary to ensure that:

i. They are well characterized and screened for infectious disease markers and
ii. They are maintained and stored as per current standards of GLP/GTP/GMP with appropriate SOPs.

The following guidelines are specifically adapted for human ES/iPS stem cell lines. However researchers are advised and expected to keep track of advances in the field.

12.3.1 Institutions that are banking or plan to bank human ES/iPS stem cell lines should establish uniform guidelines to ensure that donors of biological material give informed consent through a process approved by the IC-SCR and IEC and

meticulous records are maintained about all aspects of cell culture. Uniform tracking systems and guidelines for distribution of cells should be established as per accepted standard procedures.

12.3.2 Any facility engaged in obtaining and storing human ES/iPS stem cell lines should follow the standard practices. These include:

12.3.2.1 Creation of clear and standardized protocols for banking and withdrawals.

12.3.2.2 Documentation requirements for investigators and sites that deposit cell lines, including:

a. A copy of the donor consent form.

b. Proof of IC-SCR and IEC approval for the procurement process.

c. Available medical information on donors, along with infectious disease screening details.

d. Available clinical, observational or other diagnostic information about the donor.

e. Personal information anonymised (such that the identity cannot be frivolously disclosed), but traceable if required.

f. Critical information about culture conditions (such as media, additives, cell passage, and safety information).

g. Available cell line characterization (such as but not limited to cluster differentiation (CD) phenotyping, karyotyping and genetic markers).

12.3.2.3 A repository has the right of refusal if prior culture conditions or other items do not meet its standards.

12.3.3 A secure system for protecting the privacy of donors where the material is assigned a unique code and all other identifiable information is stored securely at the source of origin, with details on the following:

12.3.3.1 Plans for maintaining confidentiality (such as a coding system).

12.3.3.2 A secure system for inventory track from primary cell lines to those submitted to the repository and their subsequent use.

12.3.3.3 A policy governing whether and how to deliver clinically significant information obtained through research/investigations back to donors.

12.3.4 The following Standard Operating Procedures (SOPs)/ Standard of practices should be defined and maintained:

12.3.4.1 Assignment of a unique identifier to each sample.

12.3.4.2 Procedure for derivation of stem cell lines

12.3.4.3 Process for characterizing cell lines.

12.3.4.4 Process for expanding, maintaining, and storing cell lines.

12.3.4.5 System for quality assurance and control.

12.3.4.6 Website that contains scientific descriptions and data related to the available stem cell lines.

12.3.4.7 Procedure for reviewing request applications for deposit/requisition of cell lines.

12.3.4.8 Process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).

12.3.4.9 System for auditing compliance.

12.3.4.10 Schedule of charges.

12.3.4.11 Statement of intellectual property policies.

12.3.4.12 When appropriate, creation of a clear Material Transfer Agreement or user agreement.

12.3.4.13 Liability statement.

12.3.4.14 System for disposal of material.

12.3.4.15 Clear criteria for distribution of cell lines

12.3.4.16 An approved Release Certificate to be issued with each dispatch

13.0 Procurement of Biological Material for Research:

Procurement of biological material as a source of stem cells for basic or translational research is permissible subject to approval by IC-SCR and IEC. The biological material includes foetal and placental tissues, as well as gametes, blastocysts and somatic cells.

13.1 Foetal /Placental Tissue

For procurement of foetal or placental tissue as a source of stem cells, the following guidelines should be adhered to:

13.1.1 *Termination of pregnancy (TOP)* should comply with all obligations under the MTP Act. However, TOP with a view to donate foetal tissue in return for financial or any other inducement is not permissible.

13.1.2 *Informed consent for donation*

13.1.2.1 Independent informed consent should be obtained for termination of pregnancy and for donation of the foetal material for research.

13.1.2.2 The consent for donation of foetal tissue should be obtained in advance and not just before or at the time of the procedure. The parent should be given sufficient time to take decision regarding the donation.

13.1.2.3 The consent for donation should include permission for screening of the donor for transmissible infections and obtaining family history of genetic disorders.

13.1.3 The purpose and use of donated foetal tissue should be fully explained to the parents. It should not be vague and open ended. The information sheet for the purpose should be carefully scrutinized and vetted by the IC-SCR and IEC.

13.1.4 The medical person responsible for care of the pregnant woman willing to undergo termination of pregnancy and the investigator using the foetal material shall not be the same.

13.1.5 The donor shall not have the option to specify the use of the donated material for a particular person or in a particular manner.

13.1.6 The identity of the donor should be kept confidential. Personal information of the donor, however, should be kept available for traceability in situations where the cells derived from the donated foetal tissue are proposed to be used for therapy.

13.2 Gametes, Blastocysts (Pre-implantation Embryos) or Somatic Cells for Generation of Human ES/iPS Cell Lines

13.2.1 The IC-SCR and IEC, should review and approve the process of procurement of gametes, blastocysts, or somatic cells for the purpose of generating new human ES/iPScell lines. IC-SCR and IEC should verify that the blastocysts obtained from infertility clinics are in excess (spare embryos) of the clinical need of the couple.

13.2.2 Creation of human ES cell lines from blastocysts and iPS cell lines from somatic cells should be approved by IC-SCR and IEC. However, creation of the same

through IVF or other methods, specifically for research purposes, should have prior approval of NAC-SCRT through IC-SCR and IEC.

13.2.3 Consent for donation of blastocysts for establishment of human ES cells lines should be obtained from the donor at least 24 hours in advance and not at the time of the donation. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

13.2.4 There should be no inducement for donation of gametes or embryos by way of payment or in lieu of medical services, except for reimbursement of reasonable expenses for travel and loss of wages incurred by the person (amount to be decided by IC-SCR/ IEC). Similarly, no payments should be made for donation of somatic cells for use in SCNT or creation of iPS cell lines except for reimbursement towards travel expenses for attending the clinic.

13.2.5 The attending physician responsible for the infertility treatment and the investigator deriving or proposing to use ES cells shall not be the same individual. To facilitate autonomy of the donor, decisions related to the creation of embryos for infertility treatment should be independent of the influence of investigators who propose to derive or use ES cells in research.

13.2.6 *Informed consent for donation* should include:

13.2.6.1 A statement that the blastocysts or gametes will be used to derive human ES cells/cell lines for research purposes.

13.2.6.2 A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of cells derived from it.

13.2.6.3 An assurance that the investigator will follow the ethical practices for procurement, culture, and storage of cells and tissues.

13.2.6.4 A statement that the derived ES cell line may be used for development of new drugs/diagnostics or other uses which may have commercial value, but no direct financial benefit will accrue to the donors.

13.2.6.5 A statement that derived stem cells or cell lines and the information related to them may be archived for 10 years or more.

13.2.6.6 A statement that research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous transplantation.

13.2.6.7 A statement that neither consenting nor refusing to donate gametes/embryos/somatic cells for research will affect the quality of present or future medical care provided to potential donors.

13.2.6.8 A statement of the risks involved to the oocyte donor and acceptance of the responsibility to provide appropriate health care and compensation in case any complication arises during/or anytime after the procedure.

13.2.7 Identity of the donor shall be kept confidential at all times. Wherever traceability of the stem cells is required, the same shall be kept secured to ensure confidentiality. The investigator shall also document the process of maintenance of the confidentiality of any coded or identifiable information associated with the cell lines.

13.2.8 The IC-SCR and IEC while reviewing and approving the proposals for gamete/blastocyst/somatic cell donation shall ensure that the subjects do not belong to vulnerable groups.

13.2.9 There shall be no coercion to undertake human ES cell research or any activity related to SCR. Autonomy of the researcher/physician must be respected.

14.0 International Collaboration

14.1 National guidelines of respective countries shall be followed.

14.2 All international collaboration will be permitted as per the approved procedure of funding agencies (DST, DBT, ICMR etc.) or the Health Ministry's Screening Committee (as per GOI Guidelines), following joint proposal with appropriate MOU.

14.3 In situation involving a conflict (scientific and/or ethical) between the collaborators, the Indian ethical guidelines and regulations shall prevail for the work to be carried out in India.

15.0 Exchange of Biological Material for Research

15.1 All proposals for import/export of stem cells and their derivatives required for research and development including for clinical trials shall be examined by the IC-SCR, and if felt necessary by the NAC-SCRT. After satisfying the scientific and ethical considerations, the statutory requirements of approval from DCGI and the Govt. of

India's guidelines (Circular No. L/950/53/97-H1 (Pt.) dated November 19th, 1997 of the Ministry of Health) on import/export of biological materials should be followed.

15.2 A critical limitation of the use of stem cells for research and development is to maintain them in a viable state. Since their viability can be affected by X ray – irradiation, appropriate international guidelines need to be followed for their packaging, labelling, handling and transport at ports without compromising their quality.

15.3 Transport of hematopoietic stem/progenitor cells from established bone marrow/cord blood banks for unrelated donor transplantation required for therapeutic indications should follow the established procedures.

16.0 Public Participation

16.1 An interactive portal on the web shall be created by NAC-SCRT, both for the public as well as scientists and professionals to provide reliable and up-to-date information about recent developments in the field. The portal will encourage suggestions and feedback for continuous improvement.

16.2 To create awareness and update about the stem cells and their applications, periodic interactions with the public/stakeholders will be held across the country by the experts and regulators. The focus of such interactive sessions will be to educate the masses so as to avoid their exploitation and to provide a forum for free and frank exchange of views.

17.0 Periodic Review of Guidelines

The field of stem cells has seen rapid strides both in basic and translational aspects. With the unfolding of new developments and knowledge, it is essential to periodically review and update the guideline document. Accordingly periodic changes to specific clauses and sections will be notified in the form of amendments. It is one of the assigned functions of the NAC-SCRT to determine the need and mechanism for implementing revisions to the document.

References for Further Reading

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Annexure - I

Function of NAC-SCRT and IC-SCR

The National Apex Committee for Stem Cell Research has been established by Department of Health Research (DHR), Ministry of Health and Family Welfare, Govt. of India. The committee periodically assesses the adequacy of the guidelines proposed in this document and also provides a forum for continuing discussion of issues involved in hES/hiPS cell research in the light of ever growing advances in science. The committee also reviews and approves specific research protocols falling under restricted category or as provided in the guidelines. It also addresses new unforeseen issues of public interest from time to time. The body is independent and should be respected by both the lay and scientific communities. The IC-SCR shall function at the institutional level and have appropriate expertise as suggested to support this effort, and shall registered with and report to the NAC-SCRT.

1.0 National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)

This is a multidisciplinary committee with a Secretariat. It will have two main functions:

a) General oversight of the field of stem cell research and therapy in India and formulation of policy related to it

b) Review of specific controversial or ethically sensitive research and proposals for therapeutic use of stem cells/differentiated derivatives

1.1 Scope

1.1.1 The Committee has the responsibility to examine scientific, technical, ethical, legal and social issues in the area of stem cell or their derivatives based research and therapy.

1.1.2 Maintain a register of all institutions involved in any type of stem cell research and therapy including details of their IC-SCR.

1.1.3 Review annual reports of these IC-SCRs for compliance with national guidelines and ethical practices.

1.1.4 NAC-SCRT shall approve, monitor and oversee research in the restricted areas as given in this document.

1.1.5 Use of chimeric tissue for research shall be reviewed by NAC-SCRT

1.1.7 NAC-SCRT shall review and update the national guidelines for stem cell research and therapy periodically, considering scientific developments at the national or international levels.

1.1.8 NAC-SCRT in collaboration with the CDSCO will set up standards for safety and quality, quality control, procedures for collection and its schedule, processing or

preparation, expansion, differentiation, preservation for storage, removal from storage to assure quality of human stem cells or their derivatives.

1.1.9 Respond to queries/ representations from all the stakeholders in the community (investigators, industry, R&D Institutions, entrepreneurs, media, patient groups, government agencies etc.)

1.1.10 Respond to controversial issues raised /received from NGOs, patients, individuals etc., and diverted to NAC-SCRT by other agencies (ICMR, DBT, DST, MCI, DCGI etc.)

1.1.11 Monitor any unethical practices related to stem cell research and/or therapy being followed at any organization or any individual and bring them to the notice of relevant authorities.

1.2 Membership (at least 15)

Committee composition will include Chairman, Alternative Chairman, Member Secretary, nominees from DBT, DST, CSIR, DSIR, ICMR, DCGI, DAE, MCI, DGHS and biomedical experts drawn from appropriate disciplines such as Haematology, Pharmacology, Immunology, Cell Biology, Microbiology, Genetics, Developmental biology, Clinical medicine and Nursing. Other members would include a legal expert, social scientist, and women's representative. In addition consultants/experts could be consulted / invited for specific topics and advice.

1.3 Frequency of meetings

Quarterly, but can be more frequent, if necessary.

2.0 Institutional committee for Stem Cell Research (IC-SCR)

This is a multidisciplinary body at the institutional level.

2.1 Scope

2.1.1 Institutions involved in stem cell research are required to set-up a special review board to oversee research (basic science and clinical) in this field.

2.1.2 To be registered with the NAC-SCRT.

2.1.3 Provide overview of all issues related to stem cell research at the institutional level.

2.1.4 Review and approve the scientific merit of research protocols.

2.1.5 Shall function in compliance with all relevant regulations and guidelines.

2.1.6 Maintain a register of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators and notify NAC-SCRT.

2.1.7 Facilitate training of investigators involved in stem cell research.

2.1.8 Submit annual report to NAC-SCRT.

2.2 Membership (at least 7)

The committee should include representatives of the public and persons with expertise in clinical medicine, developmental biology, stem cell research, molecular biology, assisted reproduction technology, and ethical and legal issues in stem cell research. It should have the resources to coordinate reviews of various protocols.

2.3 Guidelines for the constitution of IC-SCR

2.3.1 The Chairman must have relevant medical/scientific background and be from outside the institute with no conflict of interest (COI).

2.3.2 Members from Law, Ethics and Social Sciences must be from outside the institute and with no COI.

2.3.3 Stem cell experts, if possible from outside the institute, can be the scientific/technical members.

2.3.4 Member Secretary can be from the same institute and must not have any COI.

2.3.5 Any member having COI with a particular proposal must abstain from the discussion and decision making process of that proposal.

2.3.6 IC-SCR members must be familiar with the current bioethical guidelines and guidelines for stem cell research.

2.3.7 The quorum should consist of the following members, without which the decision should not be taken:

- 2.3.7.a Chairman, and Member Secretary (if not abstaining due to COI)
- 2.3.7.b Experts from Law, Ethics and Social Sciences
- 2.3.7.c At least one stem cell expert with appropriate expertise and no COI

2.3.8 A group of institutions may have a common IC-SCR with the approval from head of each institution if:

- 2.3.8.a It designates at least one person from each institute as member (with no COI)
- 2.3.8.b Provides details of that person to NAC-SCRT
- 2.3.8.c The designated person is present during the discussion of the proposals submitted by the institute

2.4 Guidelines for framing SOP for functioning of IC-SCR

SOP for functioning of IC-SCR must be framed including, but not limited to, the following information:

2.4.1 Constitution and functioning of IC-SCR

2.4.2 Terms of reference of members

2.4.3 Detailed review and approval process

2.4.4 Frequency of meetings
2.4.5 Monitoring and follow-up of approved projects
2.4.6 Maintenance of records

2.5 The institute under which the IC-SCR functions must ensure that the IC-SCR is always independent and appropriately competent to review the proposals being submitted to them.

2.6 It is the responsibility of the IC-SCR to ensure that the research conducted under its ambit is scientific and ethical.

2.7 The IC-SCRs fulfilling aforesaid guidelines may be registered by the NAC-SCRT.

Annexure– II

Clinical Trial Protocol for Stem Cell Therapy

The document should include study title, Phase of the study, Institution conducting the trial, Sponsor Names of the Principal Investigator and Co-investigators and brief CV of all the investigators

1. Synopsis of the protocol (Summary)
2. Introduction
3. Study objectives
4. Study plan
   a. Study design
   b. Number of patients
   c. Inclusion criteria
   d. Exclusion criteria
   e. Chart of schedule of visits and activities at each visit
   f. Ethical considerations – risks and benefits
      i. Screening phase
      ii. Treatment phase
      iii. Post –treatment phase
      iv. Withdrawal of patients prior to study completion
   g. Efficacy assessment
      i. Primary efficacy outcome
      ii. Secondary efficacy outcome
      iii. Efficacy measurements
5. Safety assessment

   Adverse Events documentation in a prescribed format
      i. Definitions
      ii. Documentation of adverse events
      iii. Reporting of serious adverse events

6. Concomitant Medications

i. Documentation of medications – name, dose, duration

ii. Intercurrent illness

iii. Prohibited medications

7. Product information, dose scheme and administration instructions

i. Product information

ii. Dose scheme

iii. Route of administration

iv. Cell preparation and administration instructions

8. Data evaluation/statistics

a. Sample size determination

b. Study population analyses

c. Efficacy analysis/methods

d. Safety analysis/methods

e. Adverse events

f. Clinical laboratory studies

9. Ethical and Administrative Issues

a. Informed consent from Patient /Parent/Relative

b. Institutional Review Board Approval

c. Data and safety monitoring board

d. Adherence to the protocol

e. Protocol amendment approval

f. Data collection, source documentation and retention of patient records

g. Accountability of Investigational drug/product

h. Monitoring of the study and audit

i. Retention of patient Records

j. IPR issues: (patent obtained/filed

10. Requirements for study initiation and completion

11. Confidentiality and publication

12. Enclosures

I. Investigator brochure including background, rationale, product details, pre-clinical study results, human trials, references and publication list and reprints

II. Case Record Form

III. Manual for efficacy assessments, safety assessments, laboratory procedures etc.

IV. Administrative approvals from the following:

a. DCGI for IND/NDA
b. IEC (of each centre)
c. Approved patient information sheet and consent form
d. IC-SCR and NAC-SCRT as applicable
e. MOU/MTA in case of National/International collaboration with transfer of biological materials
f. Funding of the project/sponsor
g. Conflict of interest declaration
h. Incentives to investigators/patients/donors
i. Post-trial benefits
j. Medical insurance coverage for SAEs
k. Sponsor's responsibility towards cost of trial/complications
l. Investigator's bio-data/acceptance

Glossary

Adult stem cell: (also known as somatic stem cell): A relatively rare undifferentiated cell found in many organs and differentiated tissues with a limited capacity for both self-renewal (in the laboratory) and differentiation. Such cells vary in their differentiation capacity, but it is usually limited to cell types in the organ of origin. This is an active area of investigation.

Blastocyst: a hollow ball of 50-100 cells reached after about 5 days of embryonic development. It consists of a sphere made up of an outer layer of cells (the trophoectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells in the interior (the inner cell mass)

Bone Marrow: The soft, spongy tissue found in the centre of most large bones that produces the cellular components of blood which is known as hematopoietic stem cells (white cells, red cells and platelets). It is also a source of mesenchymal and endothelial stem cells.

Chimera: An organism, organ, or part consisting of two or more tissues of different genetic composition, produced as a result of organ transplant, grafting, or genetic engineering.

Cell line: A cell culture selected for uniformity from a cell population derived from a usually homogeneous tissue source (as an organ)

Clinical grade: Compatible and certified for administration into humans.

Clinical Research/Trial: is a branch of healthcare science that determines the safety and effectiveness of medications, devices, diagnostic products and treatment regimens intended for human use. These may be used for prevention, treatment, diagnosis or for relieving symptoms of a disease. Clinical Research is different than clinical practice. In clinical practice one uses established treatments, while in clinical research evidence is collected to establish a treatment.

Clone: a cell or organism derived from and genetically identical to another cell or organism

Clonal: cells derived from a single parent cell

Cloning: The process of creating genetically identical copy of a biological unit (e.g. a DNA sequence, cell, or organism) from which it was derived, especially by way of biotechnological methods.

- Cloning by somatic cell nuclear transfer: involves replacing an oocyte's nucleus with the nucleus of the adult cell to be cloned (or from an embryo or foetus) and then activating oocyte's further development without fertilization. The oocyte genetically reprograms the transferred nucleus, enabling it to direct

development of a whole new organism

- Reproductive cloning: The embryo developed after Somatic Cell Nuclear Transfer (SCNT) is implanted into the uterus (of the donor of the ovum or a surrogate recipient) and allowed to develop into a foetus and whole organism. The organism so developed is genetically identical to the donor of the somatic cell nucleus.

- Therapeutic cloning: The development of the embryo after Somatic Cell Nuclear Transfer (SCNT) is stopped at the blastocyst stage and embryonic stem cells are derived from the inner cell mass. These stem cells could be differentiated into desired tissue using a cocktail of growth and differentiation factors. The generated tissue/cells could then be transplanted into the original donor of the nucleus avoiding rejection.

Consent: A process by which a subject voluntarily confirms his or her (or their next of kin/legal heir) willingness to participate in a particular study/clinical trial, after having been informed of the aims, methods, required data collection procedures and schedule, anticipated benefits and potential hazards of the study and the discomfort it may entail. Informed consent is documented by means of a written, signed and dated informed consent form. The consent besides being voluntary and informed has to be without any coercion or inducement. It can be withheld, or even withdrawn at any time, without giving any reason or prejudice to present or future treatment of the individual.

Cord blood stem cell: Stem cells isolated from the umbilical cord blood collected at the time of birth. Cord blood contains hematopoietic and mesenchymal (stromal) stem cells. Cord blood is currently used to treat patients who have undergone chemotherapy to destroy their bone marrow due to cancer or other blood-related disorders.

Differentiation: The process whereby an unspecialized embryonic cell acquires the features of a specialized cell such as a heart, liver, or muscle cell. Differentiation is controlled by the interaction of a cell's genes with the physical and chemical conditions outside the cell, usually through signalling pathways involving proteins embedded in the cell surface.

Early embryo: The term "early embryo" covers stages of development up to the appearance of primitive streak i.e., until 14 days after fertilization.

Embryonic germ cell: Embryonic germ cells are primordial germ cells isolated from the gonadal ridge of 5-10 weeks foetus (those that would become sperm and eggs).

Embryonic stem cell: cells derived from the inner cell mass up to the stage of blastocysts. These cells can be cultured indefinitely under *in vitro* conditions that allow proliferation without differentiation, but have the potential of differentiating into

any cell of the three germinal layers of the body.

Feeder layer: cells used in co-culture to maintain pluripotent nature of the stem cells

Fetus: In humans, it is a developing stage from eight weeks after conception till birth

Fetal stem cell: Stem cells derived from foetal tissue including placenta that retain the ability to divide, proliferate and provide progenitor cells that can differentiate into specialized cells. A distinction is drawn between the foetal germ cells, from which the gametes develop, and foetal somatic cells, from which rest of the organism develops.

Gamete: A mature male or female reproductive cell usually possessing a haploid chromosome set and capable of initiating formation of a new diploid individual by fusion with a gamete of the opposite sex. An egg (in the female) and sperm (in the male).

Germ cells: ova and sperm, and their precursors

Hematopoietic stem cell: A stem cell that gives rise to all red and white blood cells and platelets.

Human Embryo: It is developing stage between the times of fertilization until the end of the eighth week of gestation, after which it is known as a foetus.

Implantation: The embedding of a blastocyst in the wall of uterus. In humans implantation takes place between 7-14 days after fertilization.

Induced Pluripotent Stem Cell (iPSC): These are adult differentiated cells that have been genetically reprogrammed to an embryonic stem cell–like state by being forced to express genes and factors important for maintaining the properties of pluripotent stem cells.

***In vitro*:** Of processes or reactions taking place in a test tube, culture dish, or elsewhere outside a living organism.

***In vivo*:** Of processes taking place in a living organism

Mesenchymal stem cells: Is multipotent progenitor cells that were originally identified in the bone marrow stroma and now isolated from different sources including umbilical cord blood and adipose tissue etc.

Multipotent stem cells: The cells have the potential to differentiate into different types of specialized cells constituting a specific tissue or organ.

Pluripotent stem cell: Having the ability to give rise to all of the various cell types of the body. Pluripotent cells cannot make extra-embryonic tissues such as the amnion,

chorion, and other components of the placenta. Scientists demonstrate pluripotency by providing evidence of stable developmental potential, even after prolonged culture, to form derivatives of all three embryonic germ layers from the progeny of a single cell and to generate a teratoma after injection into an immunosuppressed mouse.

Primitive streak: a collection of cells, which appears at about 14 days after fertilization from which the foetal body plan develops

Regenerative medicine: A field of medicine devoted to treatments in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cell populations or tissues

Somatic cell: cell of the body other than gamete

Somatic stem cell: an undifferentiated cell found among differentiated cells in a tissue or organ, which can renew itself and can differentiate to yield the major specialized cell types of the tissue or organ.

Somatic cell nuclear transfer: see cloning

'Spare' embryo: An embryo created during the course of IVF treatment of the infertile couple which is not utilized for the purpose also known as **supernumerary embryo.**

Stem cells: Stem cells are undifferentiated cells with a capacity for self-renewal, proliferation and differentiation into many different types of functional cell

Stem cell Bank: A facility that is responsible for accessioning, processing, packaging, labelling, storage and delivery of appropriately defined different kinds of stem cells.

Teratoma: A tumour derived from more than one embryonic layer and made up of a heterogeneous mixture of tissues (as epithelium, bone, cartilage, or muscle.

Totipotent: Having the ability to give rise to all the cell types of the body plus all of the cell types that make up the extra embryonic tissues such as the placenta.

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(TRM Cobb)

ANNEXURE P/16

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Maneka Sanjay Gandhi
Minister
Ministry of Women& Child Development
Government of India
New Delhi – 11 001.

May 2, 2018
Dear Shri Nadda,

1. I have received a series of complaints from the family members of patients of Thallassemia who have been treated by Dr. Satyendra Katewa at Soni Manipal Hospital, Jaipur. All these patients were encouraged by Dr. Katewato undergo HAPLC – Identical HSCT treatment by indicating a high success rate of 90 to 95%. Unfortunately in all these cases, the patients expired during the treatment.

2 On receiving these complaints, I did some research on the subject and found that even at the most advanced medical institutions in USA, the success rate of this treatment is less than 30#. Therefore what Dr. Katewa promised to the patients was a clear misguidance of a criminal nature. It needs to be appreciated that the family members of patients suffering from such ailments are in a state of helplessness and therefore become extremely vulnerable when some doctor gives them a ray of hope. I don't know how such experimental treatments are allowed to be offered in Indian hospitals and whether there is any mechanism to check their efficacy in the Indian circumstances once they are allowed to be introduced. Unfortunately, these treatments are offered only by the high end private hospitals and the patients get fleeced often with no positive outcomes.

3. I request you to get their particular matter examined and take necessary action against the doctor and the hospital. Simultaneously, I also request you to have a relook at the system of approving such experimental treatments so that patients are not taken for a ride.

Yours sincerely,

SD/-
(Smt. Maneka Sanjay Gandhi)
Shr. Jagat Prakash Nadda
Hon'ble Minister of Health & Family Welfare
348-A, 'C' Wing, Nirman Bhawan
New Delhi.

(TRUE COPY)

S. No.	Name	Father Name	Disease	Date of Birth	Date of Admission	Date of Discharge	BMT	Alive or Death	Date of Death	Expense said by Dr. Satyendra Katewa	Actual Expense (Approx.)	Address	Mobile
1	Anupam Sharma	Lalit Sharma	Thalassemia	08.12.2004	2.11.2015	01.05.2016	31.01.2016	No More	01.05.2016	8-10 Lac	50 Lac	Lalit Sharma, Muskan Travels, P.C. Sharma More, Merchant Road,PO+Dist - Jalpaiguri -735101 (West Bengal)	9564333331, 8967032355
2	Yogita Sharma	Sunil Sharma	Thalassemia Intermidia	17.10.2007	25.11.2016	19.01.2017	07.10.2016	No More	19.01.2017	13-14 Lac	50 Lac	Sunil Sharma, H.No. 35, M.C. Colony, Charkhidadri - 307019 (Haryana)	8059777214
3	Diya	Navneet	Thalassemia	04.11.	18.03.	14.09.2	30.08.20	No	14.09.	24-25	40-45	Navneet Kukreja, H. No. -	9416680465

	Kukreja	Kukreja	Major	2003	2016	016	16	More	2016	Lac	Lac	416/23, Gali No. 2, Ekta Vihar, Kurukshetra, Haryana	
4	Geetika Chandrawani	Kishan Kumar Chandrawani	Thalassemia	31.03.2000	19.07.2017	15.09.2017	03.08.2017	No More	15.09.2017	17-18 Lac	40-45 Lac	64/98, Hirapath, Mansarovar, Jaipur	8823922607
5	Madhur Sachdeva	Jatindra Sachdeva	Thalassemia	17.12.2000	07.06.2016	12.10.2016	N/A	Alive	____	16-17 Lac	10-15 Lac	Jatinder Sachdeva, 228/ Sector-14, Part- 2, Urban Estate, Karnal - 132001 (Haryana)	8708689716
6	Vansh	Prem Prakash	Thalassemia	31.08.2003	Jan-16	Sep-16	26.08.2016	Alive	____	20 Lac	32 Lac	Prem Prakash, S/o- Kishan Chand, Evergreen House, 1-B-14, Near Vikas Nagar, Bundi - 323001, Rajasthan	9024956999
7	Yamini Sharma	Subhash Chander Sharma	Thalassemia Major	12.12.1997	05.09.2016	27.09.2016	19.09.2016	No More	27.09.2016	30 Lac	24 Lac	C-502, Saransh Apt., 34 I.P.Extn, Patparganj, Delhi-110092	9891053169

8	Mithi Verma	Vivek Verma	Thalassemia	15.04.2011	10.04.2016	22.09.2016	29.08.2016	No More	22.09.2016	16-18 Lac	45 Lac	Vivek Verma S/o- Late R.P. Verma, 22 C, Geeta Bhawan Chowk, Sonipath - 131001 (Haryana)	9812103283
9	Krishna Agarwal	Pankaj Kumar Agarwal	Thalassemia Major from Beginning	27.01.2002	Apr-16	Oct-17	31.08.2016	No More	21.12.2017	25-30 Lac	2-3 Crore	Diamand Apartment, 95-Boro Shiv Tolla Main Road, Flat No. 2A, Block - III, Kolkata - 700038 (West Bengal)	9339723172

(True Copy)

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ANNEXURE P-18

TRUE TRANSLATED

FIRST INFORMATION REPORT

(under Section 154 Cr. P.C)

1. District JAIPUR CITY PS VIDHYASAGAR, Year 2018

2. FIR No. 0325, Date and time of FIR 28.06.2018 22:25 hrs

Act(s)		Section(s)
(i)	IPC 1860	304
(ii)	IPC 1860	420
(iii)	IPC 1860	386
(iv)	IPC 1860	120B

3. Occurrence of Offence:

(A) Day: Middle of the day date from 01.04.2016 to 01.06.2017,

time period time from: hrs time to hrs

(B) Information received at PS dated 28.06.2018 time 22:00 hrs

(C) Daily Diary Reference : Entry No. 055, dated 28.06.2018 time 22:25 hrs

4. Type of Information : WRITTEN

5. Place of Occurrence:

(a) Direction and Distance from PS 1.0 km Beat No.

(b) Address: Manipal Hospital, Vidhyadhar Nagar

(c) In case, Outside the limit of the Police Station:

Name of PS District

6. Complainant / informant:

(a) Name: AMIT KUMAR AGARWAL

(b) Father's NameSHRI MOHAL LAL AGARWAL

(c) Birth year 1975

(d) Nationality : INDIA

(e) UID NO.

(f) Passport No. Date of Issue; Place of Issue

(g) In details of (Ration Card, Voter ID Card, Passport, UID NO., Driving License, Pan)

S.No.	ID Type	ID Number

(h) Occupation

(i) Address (present): 102, NARAYAN PLAZA EXHIBITION RAOD, GHANDHI MAIDAN, PATNA, BIHAR, INDIA

Address (Permanent): 102, NARAYAN PLAZA EXHIBITION RAOD, GHANDHI MAIDAN, PATNA, BIHAR, INDIA

(j) Phone Number Mobile No. 91-9939665769

7. Details of Known/Suspect/Unknown accused with full particulars (attach separate sheet if necessary

S.No.	Name	Alias	Relative name	Address

8. Reason for delay in reporting by the complainant/informant: NO DELAY

9. Particular of the properties stolen/involved (attaché separate sheet if necessary): Sl. No Property Type (Description), Est. Value (Rs.), Status

S. No.	Property Category	Property type	Description	Value

10. Total Value of property stolen:

11. Inquest Report / UD case No., if any

S. No.	UIDB Number

12. FIR contents (attaché separate sheet, if required)

To, the SHO, Police Thana Vidhyadhar Nagar, Jaipur North. Subject: request for register of FIR. It is requested that I Amit Kumar Agarwal s/o Shri Mohan Lal Agarwal R/o 102, Narayan Plaza, Exhibition Road, Patna-1, PS Gandhi Maidan residing on aforesaid address and my cousin Krishna Agarwal that he under the disease sick with the thelissimia. One of the Dr. Satyender Kateva visited to the Hospital at Patna, that he contacted with me and said the treatment of the disease through by transplant of Haplo stem cell transplant is available and he just returned from the foreign country after completing the training concerned to this treatment and for the disease this type of treatment for thalassemics is having adequate

treatment with the success ratio of 90-95% without any risk of side affect. He influenced me with the motivational theory said that I convinced to went there at the hospital in the month of April 2016 and admitted the patient at Manipal Hospital under prevention of Dr. Satyendra Kateva at Jaipur and after admission of my child, I realized there are some of the quantity of the children after the treatment were died by Haplo stem cell transplant process and having no doubt that I realized about Dr. Satyender Kateva wrongly motivated me with the false facts and only to influence me the ratio of the successes of the children after treatment 90 to 95 % falsely convinced me and before the starting of the treatment Dr. Satyender Kateva estimated the expenses of the treatment in amount about 20-25 lakh rupees and the entire cost of the treatment can be possible to reach around 2.5 Crore. Dr. Satyender Kateva from the Hospital of Manipal showing fear of children's death taken huge money in lakh because he said to me that the medicine in lakh imported by the agent from the foreign country and ultimately the children there died that I have seen. In this way, the doctor Satyendra Kateva's lied to plan

and conspiracy to mislead me in the name of treating badly the child and during the whole treatment we noticed that 20/25 children died there in the hospital. I Sunil Sharma S/o of Om Prakash Sharma, House Number 568 Sahu Nagar Sawai Madhopur, Rajasthan, Police Station Sawai Madhopur Rajasthan, currently address House No. 35 MC Colony Charkhi Dadri Haryana Pin No. 1277306, Police Station Charki Dadri, Haryana, Mobile Number 80 5977 7214 and my daughter, whose name was Yogita Sharma, who was suffering by thalassemia intermedia disease prior to meeting she purified the blood transfusion three times in the year but the doctor Kateva, advised about the deceased can be increase the quantity for demand of the blood transfusion and after the crossing of this age more than presentage blood transfusions requried. I came in contact Dr. Satyendra Kateva in October 2015, for this disorder and requested suggestion for her treatment that he advised me for the treatment of thalassemia intermedia disease with assurance of 95% guaranteed treatment to my daughter and can be possible to spend Rs. 13 to 14 lakh, therefore, after our decisions the treatment started for our daughter

from April 2016 which says January 2017. Doctor Satyendra Kateva went to see this girl mistreated our daughter that I concerned mistakenly. I noticed 50% of the children in the hospital died during treatment who had done Halo stem cells transplant, Doctor Satyendra Kateva wrongly mislead regarding our daughter had thalassemia intermedia disease. He had to give normal blood once a year but the doctor told us, this will increase in future for having a substitute treatment of hello stem cell transplant. If you do not have a hello stem cell transplant, then it may even die your daughter in the future may be cause is expected. We got scared and ready for treatment and I was told about ₹ 13 lakhs expenditure but Dr. Satyendra Kateva increased the amount of treatment Rs. 45 to 50 lakh rupees because the costly medicine imported through by agent from the foreign country that is spent around 10-15 lakhs rupees and around 27-30 lakh paid to the hospital through net banking. The record of the expenses of the children along with my daughter kept by the Doctor Satyender Kateva of Manipal Hospital and is expected that to destroy the record for escaping safely this heinous criminal

activity, and we are requesting you to seize the record without any wasting of time. It is now requested you to register the FIR against the Dr. Satyender Kateva and the Manipal Hospital because we are having full knowledge for the conspiracy to earned huge amount with the false promise for treatment of thalassemia intermedia disease the children and so many children during course of treatment died there in the hospital of Dr. Satyender Kateva at Manipal Hospital. We are most humbly requesting you to take appropriate action the said Manipal Hospital. Yours faithfully, Sd/- the complainant dated 28.06.2018 mobile no. 9939665769, Amit Kumar Agarwal, Sunil Sharma Mobile NO. 8059777214. This is to verify that the aforesaid written complaint lodged by aforesaid Shri Amit Kumar Agarwal, address 102, Narayan Plaza Exhibition Road, Ghandhi Maidan, Patna, Bihar, India and Shri Sunil Sharma S/o Shri Om Prakash Sharma caste Brahman, aged 46 years R/o 5/368 Sahu Nagar PS Kotwali Sawai Madhopur presently 35 MC Colony Charakhi Dadri, PS Charkhi Dadri District Charkhi Dadri Haryana, physically present there at the Police Station for lodging of our complaint with requested to register

FIR. Report of police action and charges are registered under FIR section 304/420/386/120B IPC vide FIR No. 325/18 in diary then uploaded in computer and copy of the computerized complaint through hand of constable on duty sent by CI SHO and relevant documents send to the concerned officer by post. Typed by and Checked by DO.

13. Action taken (since the above information reveals commission of offence(s) u/s as mentioned at item No. 2:

(i) Registered the case and took up the investigation or

(ii) Directed /Name of the IO: RADHA RAMAN GUPTA Rank Inspector to take up the investigation or

(iii) Refused investigating due to : or

(iv) Transferred to PS (name) on point of jurisdiction.

FIR read over to the complainant/informant, admitted to be correctly recorded and a copy given to the complainant/informant, free of cost

R.O.A.C:

14. Signature/thumb impression of the Complainant/informant

Sd/-

Signature of Officer

Name: RADHA RAMAN GUPTA

Rank SI

No.29870017

15. Date and time of dispatch to the court

TRUE COPY

ANNEXURE P-19

TRUE TRANSLATED

FIRST INFORMATION REPORT

(under Section 154 Cr. P.C)

1. District JAIPUR CITY PS VIDHYASAGAR, Year 2018

2. FIR No. 0326, Date and time of FIR 29.06.2018 19:16 hrs

Act(s)		Section(s)
(i)	IPC 1860	304
(ii)	IPC 1860	386
(iii)	IPC 1860	420
(iv)	IPC 1860	468
(v)	IPC 1860	120B

3. Occurrence of Offence:

Day: Middle of the day date from 19.072017 to 15.09.2017,

time period time from: hrs time to hrs

(b) Information received at PS dated 29.06.2018 time 18:00 hrs

(c) Daily Diary Reference : Entry No. 054, dated 29.06.2018 time 19:16 hrs

4. Type of Information : WRITTEN

5. Place of Occurrence:

(a) Direction and Distance from PS 1.500 km Beat No.

(b) Address: Manipal Hospital, Vidhyadhar Nagar

(c) In case, Outside the limit of the Police Station:

Name of PS District

6. Complainant / informant:

(a) Name: SMT. LAXMI CHANDWANI

(b) Husband's Name SHRI KISHAN KUMAR CHANDWANI

(c) Birth year 1976

(d) Nationality : INDIA

(e) UID NO.

(f) Passport No. Date of Issue; Place of Issue

(g) In details of (Ration Card, Voter ID Card, Passport, UID NO., Driving License, Pan)

S.No.	ID Type	ID Number

(h) Occupation

(a) Address (present): 64/98 HEERAPATH, MANSAROVAR, JAIPUR CITY SOUTH, RAJASTHAN, INDIA

(b) Address (Permanent): 64/98 HEERAPATH, MANSAROVAR, JAIPUR CITY SOUTH, RAJASTHAN, INDIA

(i) Phone Number Mobile No.

7. Details of Known/Suspect/Unknown accused with full particulars (attach separate sheet if necessary

S.No.	Name	Alias	Relative name	Address

8. Reason for delay in reporting by the complainant/informant: NO DELAY

9. Particular of the properties stolen/involved (attaché separate sheet if necessary): Sl. No Property Type (Description), Est. Value (Rs.), Status

S. No.	Property Category	Property type	Description	Value

10. Total Value of property stolen:

11. Inquest Report / UD case No., if any

S. No.	UIDB Number

12. FIR contents (attaché separate sheet, if required)

Direction from the Metropolitan City Magistrate – No. 19, Metropolitan City Magistrate of Jaipur order for registering the case no. _____/2018 in the matter of the complaint under section 196 Cr. P.C. register by the complainant Smt. Smt. Laxmi Chandwani W/o Shri Kishan Kumar chandwani, Caste Sindhi, Aged 42 years, R/o 64/98 Heerapath Mansarovar Jaipur Rajasthan versus 1. Dr. Satyendra Kateva aged 46 years of Manipal Hospital, Seekar Road, Jaipur R/o 29A Ajmera Garden Kings Road, Jaipur. 2. Manipal Hospital, Seekar Road, Jaipur R/o 29A Ajmera Garden Kings Road, Jaipur, officers and the directors, 3. Concerned to the offence other known and unknown accused framed under the criminal charges under section 302/304/386/420/468/34/120B IPC for the crime under Organ Transplant Act, and the case registered there at Police Station Vidhyadhar Nagar, Jaipur (North). That on behalf of the complainant the complaint submitted with the following ascription: 1. The daughter of the applicant named Reetika Chandawani, who is suffered when she was around 11

months old with the disease of the thalassemics is bring there in knowledge to the mother as applicant , the daughter has been diagnosed with thalassemia due to which the blood is not being produced in her body and due to this disease she is slowly affected its organs failure adversely. After knowing this about her daughter suffered with the disease of thalassemics she went to talk with their several social organizations, so that with the hope of arrangement of unit of blood for her daughter, she could get free blood that is required every month for her girl child Geetika Chandravani. She knowingly, went to contact the society for arrangement of the blood required one unit every month so that her daughter for thalassemia disorder could be controlled, due to illness of her daughter's she also urged social organizations to set up a unit blood on regular basis for requirement of every month. Life was continuously running this way that she had to go to the hospital every month to transplant blood for her daughter Reetika Chandawani, which was very painful for her. Initially, the development of the child was sound, growing perfectly even in study but after the disease she negatively affected with the disease. 3.

The applicant due to the disease that is affected she now become in a touch to the so many social organization contacted him for the knowledge of the disease can how to prevent from this disease and over this sequence once through by the advertisement know about the Dr. Satyendra Kateva to cure the disease of thelisemia disorder. Hence, the complainant after knowingly about Dr. Satyendra Kateva, in year 2015 contacted him for treatment of her daughter Reetika Chandawani and explained about the disease of her daughter to Dr. Kateva then Dr. Kateva there at Fortis Hospital, Gurgaon suggested some of the tips. 3. The complainant when turned to went there at Fortis Hospital there at Gurgaon and meet to Dr. Kateva, explained about disease of her daughter, he assured to the complainant and explained that he returned back from foreign country after completion of the certain course of thelismia disorder and having an experience for the guaranteed treatment of thelismia disorder, convinced to the mother of the Reetika Chandawani for the treatment and given detail plan to the complainant in written on letter pad of the Fortis Hospital and said how can he cure the disease of thelisimia disorder.

That during the treatment of the patient there is a provision of the transplant of the heplo stemils transplant, he explained. 4. That during the discussion with Dr. Satayendra Kateva, he explained to the complainant if she consider the treatment the chances of death there is zeroed and thalassemics disorder can be fully rectify from this treatment to the patient and the cost of the treatment that consequently in amount of Rs. 18 to 20 lakh can be impact your financial budget. Therefore Dr. Kateva explained in written a detail format given to the complainant and said the treatment there to be coursed there at Jaipur. 5. When the complainant contacted to the Doctor, the daughter Geetika was fit by health in condition and due to the disease of the thelisimia no any problem she faced difficulties except this impact of the disease of thelisimia is signing. The amount of the expenses of treatment when she realized replied to the Doctor Satyendra Kateva with inability to bear the cost of the treatment and said no need to take your consultancy for treatment of the thelisimia. Therefore Dr. Kateva convinced to the husband and daughter of the complainant for betterment if they treat the disease of

thelesima within the time frame otherwise may be possible to cause death of the patient possible in any time because this age is perfect for the treatment of the thelisima, the doctor in continuation in touch to the parents of the patient and always intended to brief, if you are deny for the treatment that may be possible within some of the month your daughter can be die and he also said that the treatment of the thelisimia disorder is perfect and guaranteed to cure your daughter from this disease. Dr. Satyender Kateva by false promise influenced the parents of the patient daughter with hope to cure the disease through way of this treatment that he provide with the best otherwise your daughter may be expected to die in few month and the treatment is assured to cure the disease of thelisimia disorder of your daughter, believe me. The complainant realized that the accused doctor absolutely known about the treatment can be sure to the risky in life can be possible death and he was even 5% not sure for curing the patient but only for the purpose of the experiment, the doctor influenced the parents with the false promise wanted to earn money from this source only. The accused severally with the

horror impact of the disease shown to the parents and every time collected money in lakh from the parents of the patient daughter. The doctor accused by his profession have to know better the transplant of blood can be also a source to alive the girl in this disease but he with the wrong intention only for laboratory test of the disease and experiment for earning of money convinced the complainant for the treatment and earned several lakhs of money from this false promise. The staff and officer of the Manipal Hospital also are supporting hand of the doctor Sateyendra Kateva for wrongly intensified to the patient for earning of money. That during the course of treatment for the reason to asked the parents of the patient about "where is janampatri of your daughter, how not you going to the pandit for better advise and now say to me which one medicine is suitable to continue to your daughter for curing of the disease" is also proved that the doctor was not sure for treatment that certainly the death can be possible to occur in any time. The doctor of Manipal Hospital only had an intention to earn the money with the trick with false promise. So, the accused are responsible for this aforesaid criminal act and the

charges must be impose under section 302/304/386/420/468 and 34/120B IPC. 12. On this way, the complainant complained about this matter at the Police Station, Vidyadhar Nagar in Jaipur, requesting an FIR to be lodged but the SHO of the police station was not registered the case at Vidyadhar Nagar, on which the complainant had complained to the higher authority through a register letter sent on dated 29.05.2018 at, Vidyadhar Nagar, DCP office, Jaipur by registered post with request for registering an FIR against the accused in criminal prosecution act. The complainant through this way is necessary to sent registered letter because the SHO of the certain police station deny for registering of FIR against the accused. The accused by taking his hoax, by misusing the treatment, the wrong work of the transplant was done there at Manipal Hospital is absolute criminal offence and under chargeable that is requested to register FIR against the aforesaid accused. The Manipal Hospital situated there Sikar Road is located in Jaipur and this place comes under the jurisdiction of Thana Vidyadhar Nagar, Jaipur. Hence the Honorable Court has the right to hear the matter. It is a request that the matter to

be sent to the Police Station, Vidyadhar Nagar, Jaipur under section 156 (3) of the Indian Penal Code for registering of FIR, and plead the accused to punish for the charges under the criminal Acts. Complainant Lakshmi Chandwani, Jaipur, dated 12.06.2018. Police Action – this is verified that under the complaint of Smt. Chandrabani husband of Shri Kishan Kumar Chandwani, Caste Sindhi, age 42 years, House number 6488 Heera Path, Mansarovar Road, Jaipur, Rajasthan, through the said registered letter the FIR imposed under section 302/304/386/420/468 and 34/120B IPC. 12 of the section of the complaint received under section 156(3) Indian Penal Code in police station Vidhyadhar Nagar, Jaipur. That after conclusion of the application the fact of the criminal offence of the request for Section 302 is not supported with the evidence so the case no. 326/201/ under section 304/386/420/468/120B IPC registered and handed over to the IO Shri Radha Raman Gupta and he is conducted the enquiry of the case according to the rule after registering of FIR. Copy of the FIR as per rule released to the concerned.

13. Action taken (since the above information reveals commission of offence(s) u/s as mentioned at item No. 2:

    (i) Registered the case and took up the investigation to RADHA RAMAN GUPTA or

    (ii) Directed /Name of the IO: RADHA RAMAN GUPTA Rank Inspector to take up the investigation or

    (iii) Refused investigating due to : or

    (iv) Transferred to PS (name) on point of jurisdiction.

FIR read over to the complainant/informant, admitted to be correctly recorded and a copy given to the complainant/informant, free of cost

R.O.A.C:

14. Signature/thumb impression of the Complainant/informant

Sd/-

Signature of Officer

Name: RADHA RAMAN GUPTA

Rank SI

No.

15. Date and time of dispatch to the court

TRUE COPY

ANNEXURE P-20

TRUE TRANSLATED

FIRST INFORMATION REPORT

(under Section 154 Cr. P.C)

1. District JAIPUR CITY PS VIDHYASAGAR, Year 2018

2. FIR No. 0456, Date and time of FIR 25.06.2018 19:28 hrs

Act(s)		Section(s)
(i)	IPC 1860	302
(ii)	IPC 1860	304
(iii)	IPC 1860	306
(iv)	IPC 1860	420
(v)	IPC 1860	468
(vi)	IPC 1860	34
(vii)	IPC 1860	120B

3. Occurrence of Offence:

(a) Day: Middle of the day date from 01.03.2015 to 01.05.2016,

time period time from: hrs time to hrs

(b) Information received at PS dated 25.09.2018 time 19:00 hrs

(c) Daily Diary Reference : Entry No. 049, dated 25.09.2018 time 19:28 hrs

4. Type of Information : WRITTEN

5. Place of Occurrence:

(a) Direction and Distance from PS 1.0 km Beat No.

(b) Address: Manipal Hospital, Vidhyadhar Nagar

(c) In case, Outside the limit of the Police Station:

Name of PS District

6. Complainant / informant:

(a) Name: SHARAD SHARMA

(b) Father's NameSHRI LOKCHAND SHARMA

(c) Birth year 1988

(d) Nationality : INDIA

(e) UID NO.

(f) Passport No. Date of Issue; Place of Issue

(g) In details of (Ration Card, Voter ID Card, Passport, UID NO., Driving License, Pan)

S.No.	ID Type	ID Number

(h) Occupation

(i) Address (present): E-1/141, CHITRAKUT, VAISHALI NAGAR, JAIPUR WEST, RAJASTHAN, INDIA

Address (Permanent): 3233, BHINDO KA RASTA MACKIND CONE, NADIPAUL BAZHAR, KOTWALI, JAIPUR CITY NORTH, RAJASTHAN, INDIA

(j) Phone Number Mobile No. 91-8107707082

7. Details of Known/Suspect/Unknown accused with full particulars (attach separate sheet if necessary

S.No.	Name	Alias	Relative name	Address

8. Reason for delay in reporting by the complainant/informant: NO DELAY

9. Particular of the properties stolen/involved (attaché separate sheet if necessary): Sl. No Property Type (Description), Est. Value (Rs.), Status

S. No.	Property Category	Property type	Description	Value

10. Total Value of property stolen:

11. Inquest Report / UD case No., if any

S. No.	UIDB Number

12. FIR contents (attaché separate sheet, if required)

Direction from the Metropolitan City Magistrate – No. 19, Metropolitan City Magistrate of Jaipur order for registering the case in the matter of the complaint under section 190 Cr. P.C. register by the complainant Shard Sharma S/o Shri Lokchand Sharma, Address (present) : E-1/141, Chitrakut, Vaishali Nagar, Jaipur West, Rajasthan, India, Address (Permanent): 3233, Bhindo Ka Rasta Mackind Cone, Chandrapaul Bazar, Jaipur versus 1. Dr. Satyender Kateva aged around 46 years, Manipal Hospital, Seekar Road, Jaipur resident of 29 A, Ajmera Garden, Kings Road, Jaipur. 2. Manipal Hospital Seekar Road,

Jaipur and Director and officers 3. Other unknown persons and accused under section 302/304/385/420/468/34/120B IPC registered there in the Police Station at Vidhyadhar Nagar, Jaipur North. Sir, the complainant mentioned in this complaint that 1. The complainant permanently residing there at the city of Jaipur and maternal uncle of the complainant residing there at Jalpaigudi, West Bengal and the son of the maternal uncle Anupam Sharma affected with the disease of the thalassemics disorder that is required the blood transplant 1 unit on the basis of every month. That the maternal brother of the complainant Anupam is one of the very much intelligent boy is always top in study and except this disease of thalassemics disorder he was fit by look and by health. The family of the maternal uncle of the complainant adjusted the life compromised with the situation of thalassemics disorder of his son Anupam and very happily they are spending family. They have to know about the thelisimia disorder is not a disease but disorder of the body there the blood cell in the body are not in adequate quantity produced according to requirement of the body so the unit of blood transplant

in every month is normal practice the condition of the patient of thelisimia disorder and some of the medicine available in the market can be control the patient and the said patient can alive normally 50 to 60 years. 2. That the complainaint by the source having in knowledge that one of the doctor there in Fortis Hospital Dr. Satyender Kateva is specialist of the disease of Thalassemics and is very famous specialist of this disease of thalassemics disorder, so the complainaint also wanted to know how about to go for the suggestion and advise to meet with Dr. Satyender Kateva in the month of March/April 2015 along with maternal uncle, there in the Fortis Hospital at Gurgaon. 3. That after meeting with the Dr. Satyender Kateva there in the Fortis Hospital at Gurgaon with the patient Anupam the doctor advised to examine some of the medical test of the patient then the Dr. Satyender Kateva briefed to the parents of the patient about the disease of the thalassemics disorder only to cure by the treatment of Heplo Stream Cells transplant that is an option to the disease on permanent basis and guaranteed treatment and advised to come to the Hospital at Manipal Hospital Jaipur. The maternal uncle

along with the patient Anupam invited to call there at the Manipal Hospital Jaipur. 4. That after four month in the month of September 2015 the complainant, Anupam, Maternal Uncle of the complainant Lalit Sharma and his wife Beena Sharma came there at Manipal Hospital and meet with Dr. Satyender Kateva. That during the discussion Dr. Satyender Kateva said this treatment is way to cure the disease on permanent basis is a guaranteed treatment of Hello cell transplant because he is specialist of this disease came after completion of the adequate training and course form the foreign country having no doubt and you are strongly recommended to admit your patient there in hospital for treatment. Dr. Kateva briefed by sketch diagram in letter pad briefed to the complainant and parents of the patient Anupam what type of theory that he used to treat the patient to adopted the type of procedure for cure of thelisimia disorder. Dr. Kateva brief by diagram to the parent of the patient and said the first two type of the system of treatment that he ignored is a reason to the chances of the success is dim to cure the patient, but the third option for the treatment that is called US. John Hobksin treatment,

he is the expert for treat to the patient for the disease of the thelisimia disorder and hope 90 to 95% sure for cure of the disease and the chances of the death is zeroed less than 5% and assured to the patient for this treatment to the parents of the patient Anupam and he advised to admit the patient that is expendable 12 to 14 lakhs with immediate effect can be compulsory to deposit the amount. On this, complainant's maternal uncle asked for time to arrange for the money, so Dr. Kateva said that we do not want to take any more time from you. You should admit to the child as soon as possible, otherwise because of the crowd, do not admit the child and doctor Kateva told us that you would be thinking that the child will continue to bleed and his life will continue but if it is not treated then the child is likely to die soon and he said that this is the right age for the treatment of the child. If you delay treatment, then the chances of death will increase and the treatment will not be able to do properly. They are scared about the junkies saying that they have mastered about 200 transplants abroad, and 90% of them have Halo stem cells transplant have proved to be effective for the children. By believing the above

mentioned facts, we are ready to take unutilized treatment of my brother Anupam. 5. In the month of November 2015, maternal uncle of the complainant along with Anupam, came to Jaipur, after which, as per direction of doctor Kateva, the patient was admitted to the Manipal hospital for treatment, whose total expenditure was stated to be 8 to 10 lakh estimated. Thus, Dr. Kateva when we came to know about this, we agreed to this treatment, the treatment of a child was started on 12th February 2016 and its helpo stem cell transplant program but during the treatment, the condition of the child became very bad and Anupam died on March 1, 2016 during course of the treatment, when the doctors Kateva's helpo stem cell transplant program was under process. 6. That after death of Anupam, I know about Dr. Satyender Kateva with false promised only having an intention to earn money to fool the parents of the patient of thalassemics disorder and motivated the parents of the patient with the horror picture of death can be sue if you do not go to treatment that he prescribed or advised to you, this is one of the heinous crime that happened by Dr. Kateva and Dr. Kateva according to the plan made a

make shift hospital Manipal Hospital influence the people with the part of the game plan to earn money 40 to 45 lakh from each patient and nothing serious about life of the patient that definitely the patient admitted there in the hospital of Manipal mostly are died due to the process of treatment and on same way Anupam die and he also grabbed by the parents of the patient Rs. 40-45 lakhs with false promised. Furthermore Dr. Kateva for the being a charge of the medicine that is imported from the foreign country through by agent grabbed 4 lakhs in cash from the parents of Anupam. Dr. Kateva took nearly 4 lakhs cash from us in the name of imported medicines through his agents, and in the name of treatment of Anupam, he looted them. The only purpose of Kateva was to earn money by fake promise to the parents of the patient. In spite of assurances given by the doctor, despite the death of Anupam, Mrs. Bina Sharma, became ill and she had neural problems due to which our maternal family was in a state of near ruination. 7. Due to this, Dr. Satyendra Kateva, the doctor, had planned in a systematic way to lie by conspiracy to death, killing our child and taking us 12 to 14 lakh

rupees in the name of treatment, by showing the fear of death of Anupam we just come to your hospital. 8. According to the information of the complainant, Dr. Kateva has also done fraud with many other people and children have also died. The observer realized that the doctor made such a blast to earn money and was constantly wasting the life of the children. The doctor used to do such things during the treatment; the parents of the patient should find that we have some other option. What a joke like this i.e. Dr. Kateva had told us that room number 103 is not empty. Today is Tuesday, you should wear an orange dress, Anupam should have an auspicious time, on Tuesdays 2:00 pm auspicious time, and on the same day we will start the treatment. He said that on Tuesday the dawn in the presence of the soul, further he said that Basant Panchami's day is good, transplant on the same day etc. If Dr. Kateva is given the guarantee of 90 to 95% of the false guarantee, then we will not go to him for any cost if do not promise for assure treatment to cure with the chances of 90 to 95% guaranteed treatment. That our child Anupam without any major difficulty spending happy life, and today he alive together with

us if we spare from this false assurance. 9. That there in Manipal Hospital Jaipur that is run by Dr. Satyender Kateva R/o 29 A Ajmera Garden, Kings Road, Jaipur, having no any facility to treat the patient of thalassemics disorder. Doctor Kateva is lying without explaining why without adequate treatment, 95% guaranteed treatment by explaining the possibility of death of Anupam is sure if you failed to treat according to my advise at this hospital, only by the need to earn money and the need to experiment killed Anupam. Dr. Kateva killed Anupam while promised with intention of fraud and fabricated influence the parents of the demise Anupam stated. Relevant to the aforesaid heinous crime by the aforesaid accused the charges liable under the section 302/304/386/420/ and 34/120B IPC imposed on accused. 10. In this way, the complainant complained about this episode to the Police Station Officer Vidyadhar Nagar in Jaipur asking to register an FIR, but the FIR was not registered by the Police Station, Vidyadhar Nagar, on which the complainant has sent a registered post to the Police Station address to DCP requested to lodge the FIR for the criminal act against the accused, on which the FIR

was not lodged against the accused Dr. Kateva. The Complainant filed a complaint case to the Hon'ble Court to take the matter about wrongful transplant carriage at Manipal Hospital Sikar Road, Jaipur, which comes under the jurisdiction of police station, Vidyadhar Nagar, Jaipur. Therefore the Honorable Court has the right to hear this matter then the court directed to the Police Station to register the FIR against the Hospital and Dr. Satyender Kateva. 11. Hence the Honorable Court has the right to hear the matter. It is a request that the matter to be sent to the Police Station, Vidyadhar Nagar, Jaipur under section 156 (3) of the Indian Penal Code for registering of FIR, and plead the accused to punish for the charges under the criminal Acts. Complainant Sharad Sharma, Jaipur, dated 10.08.2018. Police Action – this is verified that under the complaint Sharad Sharma S/o Shri Lokchand Sharma R/o 1/141, Chitrakut, Vaishali Nagar, Jaipur, through the said registered letter the FIR imposed under section 302/304/386/420/468 and 34/120B IPC registered and handed over to the IO Shri Radha Raman Gupta and he is conducted the enquiry of the

case according to the rule after registering of FIR. Copy of the FIR as per rule released to the concerned.

13. Action taken (since the above information reveals commission of offence(s) u/s as mentioned at item No. 2:

(v) Registered the case and took up the investigation or

(vi) Directed /Name of the IO: RADHA RAMAN GUPTA Rank Inspector to take up the investigation or

(vii) Refused investigating due to : or

(viii) Transferred to PS (name) on point of jurisdiction.

FIR read over to the complainant/informant, admitted to be correctly recorded and a copy given to the complainant/informant, free of cost

R.O.A.C:

14. Signature/thumb impression of the Complainant/informant

Sd/-

Signature of Officer

Name: RADHA RAMAN GUPTA

Rank SI

No.29870017

16. Date and time of dispatch to the court

TRUE COPY

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ANNEXURE P-21

Form No. III

(Rule 26)

Warrant Order

Today, the Court Uctm. No. 15 at Jaipur name Satyender Kateva, Vs. State, in case no. 109/18 vide FIR No. 137/18 to present there at court

18.06.2018: SHO Vidhadhar Nagar submitted the status report of the case diary. Notified. That on behalf the complainant is directed to appear the court in the next date of hearing that is fixed on 20.08.2018.

Sd/-

Upper Chief Metropolitan Magistrate, Number 15

Jaipur City.

The subscription of news paper Hindustan Times dated 19.03.2018 prescribed about the "City Bizman writes to PM Modi, seeks check on stem cell transplant of thalassemics" related diseases by the different people asked by the Government of India, Prime Minister, Chief Minister, Medical Council of India, Health Department, etc., in places where the children die and the complaint of Dr. Satyendra Kateva Separately, lodged by Amit Aggarwal published in the newspaper. Dr. Kateva said in his defense against fear of complaint made story by creating havoc has filed a false case at the police station against Amit Agarwal and Pankaj Agarwal. He stated in complaint that two persons sent by Amit Agawam and Pankaj Agawam demanded 5 Crore rupees and threatened. The investigator examine the case is further mentioned that the accused Amit and Pankaj have threatened to defame the Doctor Satyender Kateva through by social media, whereas in the case, the complainant Dr. Satyendra Kateva, was summoned on 17.03.2018 at 7:30 pm, but the complainant doctor Satyendra Kateva on 17 and 18 March 2018 only went to the police complaint and registered a case, it was discovered by IO the complaint about the incident having no share to the any one or

accused having a phone call between the complainant or authentic information was failed to provide the police about the incident. In spite of repeatedly saying to the investigating officer about the incident, but no witness has presented it. In this case, Amit Agawam filed a petition in Hon'ble CJM Court No. 35 on 21.03.2018 against Satenndra Kate that he earned huge amount with false promise to the people for treatment of thalessemia and made experiment on patient that the medicine that he used to import for experiment. Shri Pankaj Kumar Agarwal also field a case there at Hon'ble CJM at Court No. 35 at Patna Bihar vide case No. 763/2018 against Satyender Kateva and copy of the same is attached for your conclusion.

Concerned to the aforesaid case the representation after the enquiry and relevant documents submitted in support of the evidence and Shri Pankaj Kumar complainant also stated in mentioning case he made several complaint against the Manipal Hospital and Dr. Satyender Kateva but the Setendra Kateva also made a false case against the complainant there at Police Station that is enquiry is going on.

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That after registering the FIR No. 8/2018 dated 15.05.2018 the case is forwarded for the further action to the concerned officer and department.

Sd/-

Dated 15.05.2018

17. Refer Notice served (acknowledgement to be placed

18. Dispatched on 15.05.2018

19. No. of enclosures.

20. List of enclosures : as annexed

Sd/-
Signature of Investigating Officer.
Submitting final report/charge sheet

Name: Harnita Sharma

Police Station, Jaipur North

True Copy

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IN THE SUPREME COURT OF INDIA

Civil Original Jurisdiction

Writ Petition (Civil) of 2019

[Under Article 32 of the Constitution of India]

In The Matter of:

Amit Kumar Agarwal & Ors. ... Petitioners

Versus

Union of India & Ors. ... Respondents

APPLICATION FOR PERMISSION TO FILE LENGTHY SYNOPSIS AND LIST OF DATES

To.

THE HOB'BLE CHIEF JUSTICE AND HIS

OTHER COMPANION JUDGES OF THE HON'BLE

SUPREME COURT OF INDIA

THE HUMBLE PETITION OF

THE PETITIONER

MOST RESPECTFULLY SHOWETH:

1. This Writ Petition impugns the actions of Respondents wherein 24 children have died due to the illegal action of the Respondent No. 4 and the others respondents even after multiple representations made over a period of more than one year have failed to take appropriate action.

(4664)

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2. The facts and contents of the Petition are not repeated herein for the sake of brevity and repetition and the same may be read as part and parcel of this Application.

3. The present petition has moved for permission to file the detailed Synopsis and List of dates with this Petition as the issues involved are necessary to narrate the synopsis in detail to accommodate the facts and circumstances.

4. This application is bona fide and made in the interest of justice.

PRAYER

In the facts and circumstances stated herein above it is most respectfully Prayed that this Hon'ble Court may be pleased to:

a) permit the petitioner to file lengthy Synopsis and List of dated along with the present Writ Petition.

b) Pass such other order or orders as this Hon'ble Court may deem fit in the facts circumstances of the case.

AND FOR THIS ACT OF KINDNESS THE APPLICANT SHALL AS IN DUTY BOUND EVER PRAYER

Filed by

(SATYA MITRA)
Advocate for the Petitioner

SATYA MITRA
ADVOCATE ON RECORD
576, MASJD ROAD, JANGPURA
NEW DELHI-110014

To

The Registrar

Supreme Court of India

New Delhi
10.05.2019

Subject: Defect Curing in the matter titled "Amit Kumar Agarwal & Ors. v. Union of India & Ors. [Diary No. 15142/2019]

Madam/Sir,

This is to bring to your kind notice that the following defect was listed in the above captioned matter:

Defect No.12: Advocate May Please Clarify Regarding Nature Of Matter After Clarification Category Updated In Computer.

Explanation: The petition and the relief sought for in this matter are civil in nature. Although there are references to FIRs in the petition, this matter is civil in nature. The present petition pertains to an unapproved medical procedure being done in a non- clinical trial set up as a result of which patients have suffered loss of life and the relief sought is in the form of firstly, injunction on haplo-identical stem cell transplants being performed in any kind of set up and secondly for the Central Bureau of Investigation to investigate into critical medical procedures being done without necessary approvals of appropriate authority.

Thanking You.

Satya Mitra

Advocate for Petitioner

Date: