Applications to the Gene Therapy Advisory Committee

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<thead>
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<th>Date</th>
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</thead>
<tbody>
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</tr>
</tbody>
</table>
## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Purpose</strong></td>
<td>Page 3</td>
</tr>
<tr>
<td>2. <strong>Introduction</strong></td>
<td>Page 3</td>
</tr>
<tr>
<td>3. <strong>Procedure</strong></td>
<td>Page 4</td>
</tr>
<tr>
<td>3.1 Procedure for applying for GTAC approval for a clinical trial</td>
<td>Page 4</td>
</tr>
<tr>
<td>3.2 Procedure for applying for GTAC approval for Named Patient Use of Gene Therapy Products</td>
<td>Page 6</td>
</tr>
<tr>
<td>4. <strong>References</strong></td>
<td>Page 9</td>
</tr>
<tr>
<td>5. <strong>Appendices</strong></td>
<td>Page 10</td>
</tr>
<tr>
<td>Appendix 1: Decision tree</td>
<td>Page 10</td>
</tr>
</tbody>
</table>
1. PURPOSE

This SOP describes the procedure for applying to the Gene Therapy Advisory Committee (GTAC) for the approval of research which involves gene therapy in human subjects.

2. INTRODUCTION

GTAC is the Government agency responsible for ensuring that studies involving gene therapy are safe. GTAC is the UK national research ethics committee (REC) for gene therapy clinical research according to the Medicines for Human Use (Clinical Trials) Regulations 2004. It is the only UK ethics committee empowered to approve clinical trials of gene therapy products according to the definition given in Part IV of Directive 2003/63/EC (amending Directive 2001/83/EC). GTAC’s remit is to consider and advise on study proposals that involve gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks. GTAC is also responsible for working with other agencies that have responsibility in this field, including Research Ethics Committees (RECs), and the Medicines and Healthcare products Regulatory Agency (MHRA).

GTAC’s definition of gene therapy is:

“The deliberate introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes”

This includes techniques for delivering synthetic or recombinant nucleic acids into humans:

- genetically modified biological vectors (such as viruses or plasmids)
- genetically modified stem cells
- oncolytic viruses
- nucleic acids associated with delivery vehicles
- naked nucleic acids
- antisense techniques (for example, gene silencing, gene correction or gene modification)
- Genetic vaccines
- DNA or RNA technologies such as RNA interference
- xenotransplantation of animal cells (but not solid organs).

The 1992 report of the Committee on the Ethics of Gene Therapy (the Clothier Committee) recommended that gene therapy (genetic engineering in humans) should be limited to life threatening diseases or disorders. GTAC approval must be sought before somatic cell gene therapy (i.e. on any cell other than the sperm or egg cells) or gene transfer research is conducted on human subjects. This includes both therapeutic and non-therapeutic research. GTAC do not currently consider research proposals for germ line cell (egg or sperm) gene therapy.

GTAC considers that gene therapy has not yet developed to the stage where it can be considered as treatment; therefore all gene therapy is research. The recruitment of patients into trials must only take place following GTAC approval, and must follow the strict procedures set out by both GTAC and other clinical research regulations.
Operational Procedures for GTAC in its role as the National Ethics Committee for gene therapy clinical trials, can be accessed at

It is the responsibility of the Chief Investigator (CI) to ensure that GTAC approval is obtained prior to initiating the trial.

All other regulation and guidance governing the use of gene therapy must also be adhered to.

3. PROCEDURE FOR OBTAINING GTAC APPROVAL

The procedure for obtaining GTAC approval differs depending on the type of gene therapy trial proposed:

1. Clinical trial of gene therapy
2. Named patient use of gene therapy products

3.1 Procedure for applying for GTAC approval for a clinical trial

There is a new application via the Integrated Research Application System (IRAS) found at: https://www.myresearchproject.org.uk/ which combines the ethics application with other regulatory forms such as MHRA applications. The IRAS application form replaces the GTAC form. All UK studies must apply through this system.

From 1st May 2008, amendments to the Clinical Trials Regulations have come into force. Included in these are new arrangements for the way GTAC operates. In future, GTAC will transfer gene therapy proposals to other Research Ethics Committees, if the proposal is deemed to be ‘low genetic risk.’ This frees up GTAC to fulfil a change in its remit as a result of recommendation 8 of the UK Stem Cell Initiative (‘The Pattison Report’) to oversee the ethical conduct of stem cell clinical research. A decision tree is included in Appendix 1).

Applicants are advised to call the GTAC secretariat to notify them that application will be submitted and when.

Checklist
A copy of the following must all be submitted as part of the GTAC application:

1. Application Form (5 bound copies, 1 unbound copy, 1 electronic copy CD/email)
2. Patient Information Leaflet (PIL) and Consent Form (5 bound copies, 1 unbound copy, 1 electronic copy CD/email)
3. Full Protocol (5 bound copies, 1 unbound copy, 1 electronic copy CD/email)
4. Investigator’s brochure plus any other supporting technical information (5 bound copies, 1 unbound copy, 1 electronic copy CD/email)
5. Researcher’s short C.V.s (1 copy of each)
3.1.1 R&D and Site Specific Approval
In addition to GTAC approval, local R&D approval and site specific assessment (SSA) approval must be sought from the local NHS Trust Research and Development office for each site where the research will take place. Applications should be made using the Site Specific Information Form and R&D forms which should be created in IRAS. The forms should be submitted to the relevant NHS Trust by the Principal Investigator at each site, together with his/her CV, once the GTAC secretariat has acknowledged receipt of the application to GTAC and confirmed that it is valid. An application for R&D and SSA approval should also be made when applicants seek to add a new site to an existing study. For further information see http://www.nres.npsa.nhs.uk/

3.1.2 MHRA approval
In addition to GTAC approval and R&D/SSA approval, the Chief Investigator is required to submit a Clinical Trials Authorisation to the MHRA. For advice on how to undertake this, please consult SOP ref JRO/SOP/008 (How to submit a CTA to the MHRA).

3.1.3 When to apply
Applications to conduct clinical trials involving gene therapy must be submitted to the GTAC secretariat 60 days prior to their next full committee meeting. Applications submitted later than this will be considered at a subsequent meeting. The application should be sent to:

GTAC Secretariat
Department of Heath
Area 604, Wellington House
135-155 Waterloo Road
London SE1 8UG

3.1.4 Notification of the Committee’s Decision
The applicant will be notified of the Committee’s decision. Reasons in writing will be given for the decision and will stipulate any conditions of approval as appropriate. GTAC are required to give an opinion within 90 days of receiving a valid application (under the UK clinical trials regulations). For those techniques covered by GTAC that fall outside of regulation (e.g. antisense applications) GTAC acts as a UKECA Recognised REC, and is therefore required to provide an ethical opinion within 60 days of receipt of a valid application.

3.1.5 Reports
Successful applicants will be asked to provide a Progress Report and Safety Report annually to GTAC. These reports should be submitted on the standard NRES report forms and are accessible online at http://www.advisorybodies.doh.gov.uk/genetics/gtac/gtacprogressreportform.doc and http://www.advisorybodies.doh.gov.uk/genetics/gtac/gtacsafetyreportform.doc respectively. Alternatively they can be accessed through the NRES website (http://www.nres.npsa.nhs.uk/).

3.1.6 Amendments
To make an amendment to an already approved gene therapy clinical trial a substantial amendment form must be completed. The form is available online http://www.advisorybodies.doh.gov.uk/genetics/gtac/gtac-substantialamendment.doc. Further details can be found in SOP reference JRO/SOP/006.

3.2 Procedure for applying for GTAC approval for Named Patient Use of Gene Therapy Products

The application form can be accessed online (http://www.advisorybodies.doh.gov.uk/genetics/gtac/namedpatientuseform-oct05.pdf). Detailed guidance on how to complete the form can be found on the GTAC Department of Health (DoH) website (http://www.advisorybodies.doh.gov.uk/genetics/gtac/applicform.htm); you should ensure you check this website for up to date instructions on completing the form.

Guidance notes on completing the application form

This guidance applies to the proposed use of products that do not possess a European Marketing authorisation – GTAC do not encourage the off-protocol use of gene therapy products where compelling evidence of likely efficacy is absent.

Section 1: Required content of application

Sufficient information must be given so that GTAC are able to make a judgement about the ethical acceptability of the proposed named patient use. Applications are considered as valid if a full account of what is proposed is given.

Applications for named patient use should only be made in instances where efficacy data can be provided.

Where patients are to receive gene therapy in accordance with a GTAC approved protocol, details as to the clinical condition of the patient and the rationale for the named patient use of gene therapy for this patient must be provided. Where the investigational product has not previously been approved by GTAC, proposals for the named patient use should normally consist of:

i. Details of the gene therapy procedure and associated treatments;

ii. Arrangements for patient monitoring and follow-up;

iii. Safety and efficacy data relating to the clinical use of the specific product (as generated by the company or academic researcher providing the product for use);

iv. Patient information material and consent form;

v. Information about relevant qualifications and experience of the key staff involved in the procedure and care of the patient;

vi. Details supporting the suitability of the research centre;
vii. The application should include an appraisal of the risks to the subject and the possible benefits. This should include a summary of the alterations to normal clinical care, especially any invasive procedures and those that may be uncomfortable or inconvenient for the subject (such as procedures that involve lengthy or frequent attendance as outpatients or in-patients or requirements to remain in an isolation room). Details should be given if visits from relatives and friends are to be restricted.

The gene construct and delivery system

The proposal should describe the nature and structure of the genetic material that is to be administered and the rationale for its use. It should include:

i. an overview of the construct and its regulatory elements;

ii. the methods used to produce it, including any producer cell lines;

iii. the method of delivery;

iv. the form in which the material will be administered to the patient;

v. the dose to be administered and;

vi. details (including dosage and schedules) of any concomitant treatments.

Prior studies

Where possible, reference should be made to any previous applications to GTAC, to published studies and to guidance from GTAC or others on the safety and tolerability of the vector system in human subjects. A summary of relevant data from previous clinical trials, including peer-reviewed publications, should be submitted to support the safety and likely efficacy.

Additional clinical procedures

The application should detail the clinical procedures. This should include details of any preliminary treatments, for example surgery or chemotherapy to remove or reduce the number of abnormal cells. The procedures and regime for administering the gene therapy material should be given, including the nature and timing of administration and monitoring. Standard Operating Procedures (SOPs) should be provided and this may take the form of a standard data sheet.

Monitoring

The arrangements for monitoring subjects before and after the administration of the genetic material should be given. The application should specify the frequency and duration of monitoring, the biochemical, physiological, pathological tests to be done, and whether special post-mortem studies will be requested if a patient dies.

A reference sample of the material injected should be stored to allow for retrospective analysis. Where possible, it is also recommended that serum (and,
if feasible, cell) samples should be taken at suitable intervals and stored to provide for retrospective analysis in the event of adverse reactions.

Section 2: Information for patients and consent

Informing Patients
The research participant must be well informed about the procedures and risks involved. Although information can be given in a number of ways, the written information leaflet is particularly important and should always be provided. This should be kept as a permanent record of the key points, to which the patient can refer, and therefore a critical element in informing consent. The document also provides a source of reference for families and friends.

It is a priority for GTAC to ensure that potential participants have clearly understood exactly what is involved, particularly given the sensitivity involved with the hopes and motives of patients who have a serious disease. It is therefore advised by GTAC that appropriate independent counselling is provided wherever possible.

Consent
It is essential that appropriate informed consent is sought prior to the potential participant’s inclusion in any aspect of the study. Consent should be sought in accordance with the UK Medicines for Human Use Regulations 2004, the DoH Research Governance Framework for Health and Social Care 2005 (2nd Edition), the Mental Capacity Act 2005. For further information see consent guidance from NRES (http://www.nres.npsa.nhs.uk/applicants/help/guidance.htm#consent) and the Imperial College SOP for seeking informed consent.

Where an adult is not capable of giving informed consent, by reason of mental incapacity, then that person must be treated in accordance with his or her ‘best interests’. Under present UK law, lawful consent cannot be obtained from any health proxy, nor can the consent of the incapacitated adult be presumed.

Adults with incapacity in Scotland
Where the research participants may include adults in Scotland who are incapacitated from giving lawful consent, GTAC will be responsible for ethical approval of the trial outside Scotland, and for legally competent research participants within Scotland. In respect of the subject group of incapacitated adults, the applicant must submit the application to the relevant REC in Scotland.

Insurance
The proposal should confirm that appropriate insurance and/or indemnity is in place. As Imperial employees, Imperial indemnity must be arranged through the Clinical Research Governance Office to cover against negligent and non-negligent harm. This is in addition to the NHS Trust indemnity provided to cover against negligent harm. Where there is a commercial company involved, evidence of ABPI indemnity must also be included with the GTAC application where applicable.

Checklist
A copy of the following must be submitted as part of the application:
1. Application Form (5 copies, plus 1 electronic copy)
2. Technical appendices (5 copies, plus 1 electronic copy)
3. Patient Information Leaflet (PIL) and consent form (5 copies, plus 1 electronic copy)
4. Applicants’ C.V.s (one copy of each)

4. REFERENCES

Department of Health, Gene Therapy Advisory Committee guidance http://www.advisorybodies.doh.gov.uk/genetics/gtac/

National Research Ethics Service guidance http://www.nres.npsa.nhs.uk/


JRO/SOP/008 How to submit a CTA to the MHRA
5. APPENDICES

5.1 Appendix 1: Decision tree

1. Is this a phase III trial? 
   - YES 
   - NO

2. Is the GT-phem subject to MHRA's provisions for first-in-human (FIM) trials?
   - YES 
   - NO

3. Is the study conducted in immunocompromised individuals?
   - YES 
   - NO

4. Is the GT-phem a plasmid (or series of plasmids)?
   - YES 
   - NO

5. Is the GT-phem:
   - an integrating virus ( lentiviruses or retrovirus) or
   - a partially integrating virus (such as AAV) or
   - a replicating virus or
   - a novel virus (e.g. primate adenovirus serotype, pseudotyped or animal virus) or
   - used for evasive transduction of cells (stem cells or T-cells) with the modified cells reintroduced into the patient or
   - one which results in longer term (persistent) expression of transgene and/or vector sequences (such as with AAV) or
   - NO

6. Is the transgene:
   - a growth factor or
   - cell cycle regulating protein or
   - an anti-apoptotic or
   - coding for a protein that may result in production of auto-antibodies or
   - a gene product which, if expressed in non-target tissue, may have unintended effects (example: suicide gene)?
   - YES 
   - NO

7. Has the product been approved previously by GTAC in the same disease application and by the same method of administration?
   - YES 
   - NO

8. Is this a phase I trial?
   - YES 
   - NO

9. Is this a cancer-vaccine approach or vaccine for infectious disease where the vaccine is administered locally not systematically?
   - YES 
   - NO

Category 1 trial: GTAC will wish to review the trial (no transfer)

Category 2 trial: Transfer may be considered on a case-by-case basis at the request of the applicant.

Category 3 trial: GTAC is likely to recommend transfer unless the patient population is significantly different than with previous trials.

Category 3 trial: GTAC is likely to recommend transfer unless the plasmid codes for:
- a growth factor or
- cell cycle regulating protein or
- an anti-apoptotic or
- coding for a protein that may result in production of auto-antibodies or
- a gene product which, if expressed in non-target tissue, may have unintended effects (example: suicide gene).