Applications to the Gene Therapy Advisory Committee

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1. PURPOSE

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

2. INTRODUCTION

A GTAC is an ethics committee under the oversight of the National Research Ethics Service responsible for ensuring that studies involving gene therapy are safe. There are four UK ethics committees 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. The four committees are - London – West London and GTAC; South Central – Oxford A; North East – York; or Scotland (A) REC (based in Edinburgh).

Definition of a Gene Therapy Medicinal Product:

Gene therapy medicinal products are defined in Part IV of Directive 2003/63/EC (amending Directive 2001/83/EC) as follows:

“…[a] gene therapy medicinal product means a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.”

In addition to its legal responsibility for trials of gene therapy medicinal products, a GTAC committee also reviews the following types of research:

- Trials of other Advanced Therapy Medicinal Products (ATMPs), i.e. somatic cell therapy and tissue engineered products
- Trials of stem cell therapy involving cells derived from stem cell lines
- Trials of vaccines involving recombinant vectors or vectors with potentially immuno-regulatory mediator molecules
- First in human trials of vaccine vectors (or variants of vectors in use) or of engineered antigen molecules
- Other non-CTIMP gene therapy research (e.g. non-interventional trials).

Research studies involving well-established adult stem cell therapies (for example, bone marrow transplantation) or types of vaccine may be reviewed by any appropriate REC.
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’s do not currently consider research proposals for germ line cell (egg or sperm) gene therapy.

Guidance on gene therapy ethical review requirements can be found at http://www.hra.nhs.uk/resources/applying-to-recs/gene-therapy-advisory-committee-gtac

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 A GTAC APPROVAL

The procedure for obtaining a 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 a GTAC approval for a clinical trial

Applications are made 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 now 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 a 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 a GTAC to fulfill 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 contact the GTAC secretariat to notify them that an application will be submitted and when nrescommittee.london-westlondon@nhs.net

3.1.1 R&D and Site Specific Approval

In addition to a 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 a 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.

Imperial College AHSC has a Joint Clinical Research Safety Committee which must approve gene therapy, genetic modification and wild type non-medicinal biological agent research projects occurring at this site before submission to GTAC.

Contact Details:
Sharon Wood – Director of Safety Services
Tel: 08714 610 122
Email: sharon.wood@imperial.nhs.uk

3.1.2 MHRA approval
In addition to a GTAC approval and R&D/SSA approval, the Chief Investigator is required to submit a Clinical Trials Authorisation to the MHRA as gene therapies are classed as investigational medicinal products in law. 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 via the Integrated Research Applications System (IRAS) as part of the standard national ethics application process. The site can be accessed at www.myresearchproject.org.uk

For written correspondence the address is:

GTAC Secretariat Ground Floor, Skipton House
80 London Road
London
SE1 6LH

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. GTACs 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 a GTAC that fall outside of regulation (e.g. antisense applications) a 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 the approving GTAC. These reports should be submitted on the standard NRES report forms and are accessible online via http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/

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 via the NRES website. Further details can be found in SOP reference JRO/SOP/006.

4. REFERENCES


UK Medicines for Human Use (Clinical Trials) Regulations 2004
http://www.opsi.gov.uk/si/si2004/20041031.htm


Mental Capacity Act 2005

Human Research Authority Website
http://www.hra.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 ST-IMP subject to MHRA’s provisions for first-in-man (FIM) trials?
   - YES
   - NO

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

4. Is the ST-IMP a plasmid (or series of plasmids) or
   - YES
   - NO

5. Is the ST-IMP:
   - an integrating virus (e.g. retrovirus) or
   - a partially integrating virus (such as AAV) or
   - a replicating virus or
   - a novel virus (e.g. rare human adenovirus serotype, pseudotyped or animal virus) or
   - used for ex vivo transduction of cells (stem cells or T-cells) with the modified cells reintroduced into the patient or
   - one which results in long-term (persistent) expression of transgene and/or vector sequences (such as with AAV) or
   - YES
   - NO

6. Is the transgene:
   - a growth factor or
   - cell cycle regulating protein or
   - an anti-angiogenic 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 systemically?
   - YES
   - NO

Category 1 trial: GTAC is likely to recommend transfer unless the patient population is significantly different than with previous trials.

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

Category 2 trial: Transfer will be considered on a case-by-case basis.

Category 3 trial: GTAC is likely to recommend transfer unless the plasmid codes for either:
- a growth factor or
- cell cycle regulating protein or
- an anti-angiogenic 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).