ADVANCED THERAPY AND GENE MODIFICATION SAFETY COMMITTEE APPROVAL FOR RESEARCH

DOCUMENT NO.:	**GS012 v4.0**
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1 INTRODUCTION

1.1 The Academic & Clinical Central Office for Research & Development (ACCORD) is a joint office comprising clinical research management staff from NHS Lothian (NHSL) and the University of Edinburgh (UoE).

1.2 NHSL and UoE (ACCORD) supports the set up and/or conduct of clinical studies involving advanced therapy (investigational) medicinal products (AT(I)MPs) and gene therapy or genetically modified micro-organisms (GM, GMO).

1.3 These advanced therapy medicines for human use are based on genes, tissues or cells and are classified into three main types:

- Gene therapy medicines: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases;
- Somatic-cell therapy medicines: these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;
- Tissue-engineered medicines: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue;
- In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as combined ATMPs. An example of this is cells embedded in a biodegradable matrix or scaffold.

1.4 The risk assessment of these research studies is overseen by the Advanced Therapy and Gene Modification Safety Committee (ATGMSC), who provide expert opinion and mentorship, as required.

1.5 The Committee comprises a panel of NHSL and UoE experts from various backgrounds, and those invited to participate in the risk assessment will depend on whether the clinical study involves an AT(I)MP or a GM/GMO, in accordance with the NHSL ATGMSC Constitution and Terms of Reference.

2 PURPOSE

2.1 The purpose of this Standard Operating Procedure (SOP) is to outline the approval process for applications to the ATGMSC for research studies involving an AT(I)MP or GM(O) in NHSL, including review of any amendments to these studies.

3 SCOPE

3.1 This SOP is applicable to all clinical research studies involving an AT(I)MP or GM(O) to be conducted in NHSL. It applies to the Principal Investigator (PI) of these studies, and to their research teams.

3.2 It also applies to the ACCORD Senior Management Team (SMT), the ATGMSC Secretary, or designee, responsible for the administration of the ATGMSC, and to ACCORD Sponsor reviewers and R&D Governance staff involved in the review of research studies Sponsored by NHSL and/or UoE or hosted by NHSL.

4 RESPONSIBILITIES

4.1 The ACCORD SMT is responsible for making and documenting the decision as to whether a research study conducted in NHSL requires approval from the ATGMSC, for informing the ACCORD Sponsor reviewer or R&D Governance reviewer of this decision, and for advising the ATGMSC Secretary of the study.

4.2 The ACCORD Sponsor reviewer and/or R&D Governance reviewer is responsible for advising the PI of the process for obtaining approval from the ATGMSC (including approval of amendments, where applicable), should their research include the use of an AT(I)MP or GM(O), and for informing the ACCORD SMT of the project. They are also responsible for ensuring that ATGMSC approvals are in place for the study, and any subsequent amendments, where required.

4.3 The PI, or designee (for example Trial Manager), is responsible for;

- Providing essential trial documents for ATGMSC risk assessment review/approval (including the draft and final completed risk assessment document),
- Assessing any study amendments to determine impact on the original risk assessment, and informing the ATGMSC Secretary of the outcome of this assessment,
- Filing original copies of the Risk Assessment (GS012-F01 Form A or GS012-F02 Form B), the Risk Assessment Report and ATGMSC approval letter in the Trial Master File (TMF) / Investigator Site File (ISF).

4.4 The ATGMSC Secretary, or designee, is responsible for;

- Collating the study documentation that is required for the ATGMSC

review, where applicable, including review of amendments,
- Convening committee meetings, with appropriate membership in attendance, and distributing relevant supporting documentation for the review,
- Collating comments from non-attendees and ensuring that these are considered during the study review,
- Notifying the PI, or designee, of comments and amendments to the trial protocol and / or risk assessment raised by the ATGMSC,
- Notifying the PI, Sponsor reviewer(s) and/or R&D Governance reviewer when ATGMSC approval has been granted (or not) and/or when ATGMSC approval of amendments are required.
- Filing the electronic copies of the Risk Assessment (GS012-F01 Form A or GS012-F02 Form B), the Risk Assessment Report and ATGMSC approval letter on the NHSL R&D shared S: drive.

4.5 The ATGMSC is responsible for assessing the risks associated with the research study (including amendments where applicable), reviewing a report of their assessment and agreeing a contingency plan as appropriate.

5 PROCEDURE

5.1 The Sponsor reviewer, R&D Governance reviewer, or designee, will refer early enquiries regarding the Sponsorship or hosting of a study potentially involving an AT(I)MP or GM(O) to the ACCORD SMT for consideration.

5.2 A member of the ACCORD SMT will advise the ATGMSC Secretary, Sponsor reviewer (if applicable), R&D Governance reviewer, or designee, on the requirement for an ATGMSC review and risk assessment. This decision will also be documented in the weekly ACCORD SMT meeting minutes.

5.3 Where ATGMSC risk assessment is not required, the Sponsor reviewer or R&D Governance reviewer will continue their review of the study in accordance with SOP GS003 (Sponsorship Approval) or GS001 (R&D Management Approval), respectively.

5.4 Following notification that a study requires ATGMSC review, the ATGMSC Secretary, or designee, will send the Risk Assessment Submission document (GS012-F01 Form A: Genetically Modified Organisms or GS012-F02 Form B: Advanced Therapy Investigational Medical Products (ATIMPs), as appropriate), in addition to relevant guidance notes (GL004 or GL005), to the PI for completion.

5.5 In addition to the guidance notes provided, the ATGMSC Secretary, or designee, will provide contact details for the NHSL Biological Safety Officer to the PI, along with any further committee contacts that may need to be approached for advice on the Risk Assessment completion.

5.6 The PI, or designee, will complete the relevant Risk Assessment (RA)

Submission document (GS012-F01 Form A or GS012-F02 Form B) and submit this, with the required study documents, outlined in Appendix 1, to the ATGMSC Secretary via e-mail (loth.atgmcommittee@nhslothian.scot.nhs.uk).

The ATGMSC Secretary, or designee, will arrange a meeting of the ATGMSC following receipt of the completed required documentation, and in accordance with the NHSL ATGMSC Constitution and Terms of Reference. This will include relevant members of the Committee based on whether the study includes an AT(I)MP or GM(O), and a virtual meeting may be conducted if considered appropriate.

5.7 The ATGMSC Secretary, or designee, will forward all required documentation to the relevant ATGMSC members at least 1 week prior to the meeting.

5.8 If the completed risk assessment is not received at least 1 week prior to the meeting date, the meeting will be rescheduled.

5.9 If a committee member is unable to attend the review meeting they can provide written comments to the ATGMSC Secretary, or designee, who will circulate them to the other relevant committee members, or raise them for discussion during the review meeting.

5.10 The ATGMSC Secretary, or designee, will invite the PI, or designee, to attend the review meeting if possible, to provide clarity on any queries the committee may have.

5.11 The ATGMSC will evaluate the competency and experience of the PI and conduct a risk assessment of the AT(I)MP or GM(O), based on the information provided by the PI.

5.12 The Committee's findings will be documented in a detailed ATGMSC Risk Assessment (RA) Report, including any recommendations for mitigation and contingency planning.

5.13 The ATGMSC Secretary, or designee, will attend the ATGMSC meeting and record the minutes from which they will write up a draft RA Report. The report will detail sections of the RA that need to be addressed prior to ATGMSC approval.

5.14 The draft ATGMSC RA Report will be circulated to the ATGMSC and the PI for review for accuracy by the ATGMSC Secretary, or designee. At this point, any required amendments to the RA will be made by the PI and resubmitted to the ATGMSC Secretary, or designee, for review and approval.

5.15 Details of the RA sections that have been amended by the PI at the Committee's request will be recorded on the RA report and recirculated to the Committee for approval.

5.16 By confirming acceptance of the approved ATGMSC RA Report (via e-mail), the PI agrees to conduct the trial according to the requirements detailed within it.

5.17 The ATGMSC Secretary, or designee, will send the final approved and agreed ATGMSC RA Report to the PI. As a minimum, this will include;

- The date and time of the meeting
- Documents reviewed (including version and date)
- Decision of the meeting as follows:
    A. Approval with standard and, if necessary, additional conditions.
    B. Provisional approval with request for further information to be submitted to the committee.
    C. Non-approval with a request to resubmit and suggestions to support a better resubmission (this will be rare)

If B is chosen, the RA Report (or covering e-mail) will indicate whether the whole committee needs to see the further information (this can be done electronically), or whether the committee delegates an individual to give final approval (this could be the chair or a person with particular expertise chosen from the committee or an external expert).

5.18 The ATGMSC Secretary, or designee will retain electronic files of all studies reviewed by the ATGMSC in the NHSL R&D shared S: drive.

5.19 The ATGMSC Secretary, or designee, will inform the PI, Sponsor reviewer, R&D Governance reviewer, or designee of the ATGMSC decision and provide a signed copy of the approved RA, RA Report and ATGMSCletter of approval / non-approval, as appropriate.

5.20 For research studies Sponsored by NHSL and/or UoE, the Sponsor reviewer, or designee, can give Sponsor approval in principle prior to review/approval by the ATGMSC, and will retain a copy of the ATGMSC RA decision letter in the TMF or Sponsor File. An electronic copy will be retained in the study specific file on the ACCORD SharePoint.

5.21 Documents relating to the Risk Assessment review will be retained as follows:

(a) Risk Assessment (GS012-F01 Form A or GS012-F02 Form B) original copies to be retained in TMF/ISF by the PI, or designee. Electronic copy to be held on the NHSL S: Drive by the ATGMSC Secretary.

(b) Risk Assessment Report original copies to be retained in TMF/ISF by the PI, or designee. Electronic copy to be held on the NHSL S: Drive by the ATGMSC Secretary.

(c) Approval Letter original copy to be retained by the ATGMSC Secretary. Electronic copy to be retained on the NHSL S:Drive by the ATGMSC Secretary and sent to the PI, or designee.

5.22 The R&D Governance reviewer cannot issue NHSL management approval until review/approval by the ATGMSC in accordance with GS001 (R&D Management Approval), and will retain a copy of the ATGMSC RA decision letter in the relevant study folder on the NHSL R&D S: drive.

6 AMENDMENTS

6.1 Any amendments to the trial protocol or documents pertaining to the IMP, investigator notifications of important safety information or new Investigators conducting the study must be reviewed by the ATGMSC.

6.2 The amendment, in conjunction with the current version of the RA will be reviewed by the PI to ascertain whether the amendment will impact the content of the current risk assessment as detailed in 6.1.

6.3 The PI will notify the ATGMSC Secretary, or designee, as to whether any changes to the RA are required or not.

6.4 The PI may request, via the Secretary or designee, to consult additional Committee members for opinion and guidance at this stage.

6.5 If the PI deems the amendment to have no impact on the RA and safety of the trial within NHSL, this will be confirmed to the ATGMSC Secretary, or designee, via email.

6.6 The PI, Sponsor Reviewer (resgov@accord.scot) or the R&D Governance reviewer (R&DOffice@nhslothian.scot.nhs.uk) will be notified by the ATGMSC Secretary, or designee, via email that no review is required by the ATGMSC. This e-mail will confirm the current version of the RA

6.7 If the amendment is deemed to impact the RA and/or safety of trial within NHSL, the PI will amend the RA appropriately and submit this, and any applicable documents, to the ATGMSC Secretary, or designee, for review by the ATGMSC.

6.8 Amendment review by the ATGMSC may be done via a meeting following the procedure detailed in section 5. Alternatively, amendment review can be conducted via e-mail correspondence with the ATGMSC Secretary and members with feedback provided to the PI (see section 5.15 onwards).

6.9 Where an amendment requires review by the ATGMSC, the ATGMSC Secretary, or designee, will inform the PI, Sponsor Reviewer and/or R&D Governance Reviewer to ensure that the amendment is not implemented in NHSL before the ATGMSC approval of the amendment is in place.

6.10 Where the Sponsor Reviewer and/or R&D Governance Reviewer receive an amendment and have not received notification from the ATGMSC Secretary, or designee, they will contact the ATGMSC Secretary (or designee) and the PI to ask if the amendment has been assessed and if ATGMSC approval is required.

6.11 The Sponsor Reviewer and/or R&D Governance Reviewer will document ATGMSC approval in accordance with SOP GS011 Sponsor Approval of Amendments and GS007 R&D Review of Amendments, respectively.

7 REFERENCES AND RELATED DOCUMENTS

- NHS Lothian Advanced Therapy and Gene Modification Safety Committee Constitution and Terms of Reference.
- GS001 R&D Management Approval
- GS003 Sponsorship Approval
- GS007 R&D Review of Amendments
- GS011 Sponsor Approval of Amendments
- GS012-F01 FORM A: Genetically Modified Organisms
- GS012-F02 FORM B: ATIMPs
- GL004 Guidance Notes FORM A: Genetically Modified Organisms
- GL005 Guidance Notes FORM B: ATIMPs

8 DOCUMENT HISTORY

Version Number	Effective Date	Reason for Change
1.0	07 MAY 2020	This is the first version of this SOP.
2.0	11 SEP 2020	Minor updates made throughout the SOP, making reference to responsibilities and process for review of amendments by the ATGMSC. Additional detail added to Section 6 to clarify the process. References updated.
3.0	18 NOV 2020	Update to Amendment review responsibilities and process (section 4 & 6). The Investigator is now responsible for informing the ATGMSC of amendments and assessing the risk assessment for changes in line with amendments.
4.0	24 MAR 2022	Minor update to include the issue of guidance notes (GL004 and GL005) to the PI, alongside the Risk

		Assessment Form. Update to committee email address. Minor administrative changes to GS012-F01 and GS012-F02 (both now v3.0)

9 APPROVALS

Sign	Date
Heather Charles Heather Charles (Mar 8, 2022 08:54 GMT) AUTHOR: Heather Charles, Head of Research Governance, NHS Lothian, ACCORD	Mar 8, 2022
Fiona McArdle Fiona McArdle (Mar 8, 2022 08:55 GMT) APPROVED: Fiona McArdle, Deputy R&D Director, NHS Lothian, ACCORD	Mar 8, 2022
Gavin Robertson (Mar 8, 2022 08:46 GMT) AUTHORISED: Gavin Robertson, QA Coordinator, NHS Lothian, ACCORD	Mar 8, 2022

Appendix 1 Essential Documents for ATGMSC Review

Prior to ATGMSC Approval:

- Protocol and Subsequent Amendments
- Investigator Brochure / Drug details
- Research Ethics Committee (REC) application and subsequent amendments (if submitted application is available at the time of review)
- Relevant publications
- Curriculum Vitae (CV) of PI and other relevant Investigators
- Completed ATGMSC Risk Assessment form (GS012-F01 FORM A or B)
- Evidence of GCP training by the study team (as soon as available)
- Evidence of BLS/ALS training (as appropriate)
- Documents submitted to GTAC (gene therapy only)
- GTAC letter indicating favourable opinion (gene therapy only)

Prior to Study Start (as above plus):

- REC favourable opinion
- R&D Management Approval
  N.B this confirms that the MHRA clinical trial authorisation is granted and that the clinical trial agreement is in place (CTIMPs).
- ATGMSC approval letter
- Copy of approved ATGMSC Risk Assessment Report, signed by the Chair,
- Signed and completed Service Level Agreement
- Patient Information Sheets
- Consent Forms

GS012 Advanced Therapy and Gene Modification Safety Committee Approval for Research v4.0

Final Audit Report 2022-03-08

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