

Review

QJM

Standards for gene therapy clinical trials based on pro-active risk assessment in a London NHS Teaching Hospital Trust

K.B. BAMFORD¹, S. WOOD² and R.J. SHAW³

From the ¹Department of Infectious Diseases and Microbiology, Imperial College, and Division of Microbiology, Hammersmith Hospitals NHS Trust, London, ²Universal Safety Consultants Ltd, London, and ³Medical Director's Office, Hammersmith Hospital, London, UK

Summary

Conducting gene therapy clinical trials with genetically modified organisms as the vectors presents unique safety and infection control issues. The area is governed by a range of legislation and guidelines, some unique to this field, as well as those pertinent to any area of clinical work. The relevant regulations covering gene therapy using genetically modified vectors are reviewed and illustrated with the

approach taken by a large teaching hospital NHS Trust. Key elements were Trust-wide communication and involvement of staff in a pro-active approach to risk management, with specific emphasis on staff training and engagement, waste management, audit and record keeping. This process has led to the development of proposed standards for clinical trials involving genetically modified micro-organisms.

Introduction

Hammersmith Hospitals NHS Trust (HHNT) has used a risk assessment process to develop safe systems and practices for clinical trials of new gene therapy agents. To put in place an environment, systems and processes that have allowed gene therapy to proceed, has involved multidisciplinary, Trust-wide planning with in-depth consideration of a wide range of issues, and a pro-active problem-solving approach to risk management. The result has been the development of a motivated skilled team with a clear understanding of why practices and policies are in place, and a commitment to their adherence. The time and effort spent on the risk management process has made it possible to undertake an ongoing programme of gene therapy trials in this Trust, with the support of the regulatory bodies, the confidence of patients

and staff, and has resulted in the development of a set of standards applicable to all such trials.

Background

Successful gene therapy relies on delivery of the therapeutic gene to the target organ or disease site.¹ Genetically modified micro-organisms (GMMs)—in particular viruses, but also other candidate delivery vehicles modified to reduce virulence or infectivity—are most frequently used as vectors. There are other vectors that may present advantages as gene therapy agents in the future. For example, plasmids or liposomes, where if the disadvantages currently associated with clinical efficacy and delivery are overcome, future risk assessment will probably

Address correspondence to Dr K.B. Bamford, Division of Microbiology, Hammersmith Hospitals NHS Trust, Du Cane Road, London W12 0NN. e-mail: k.bamford@imperial.ac.uk

QJM vol. 98 no. 2 © Association of Physicians 2005; all rights reserved.

indicate many safety advantages. Currently viruses have an advantage, as they are naturally able to enter cells, often specifically targeting certain cell types, and use many of the normal cellular pathways for metabolism. Viruses can be genetically altered to carry a specific gene, e.g. a cytokine to stimulate the immune system, or to introduce a 'normal' human gene, which will potentially improve disease outcome, by manipulating the local cellular physiology.⁸ This approach presents a range of issues which have to be considered before such organisms can be used as therapeutic agents.²⁻⁷

On one side of this equation is the exciting potential to treat a patient who has come to the end of other conventional treatment options. On the other side, the patient may be at risk of disseminated infection from the GMM if they are in an immunocompromised state. Visitors and relatives, as well as social contacts before and after patient discharge must be protected from any secondary infection. Staff either directly caring for the patient, involved in preparing GMMs, or handling patient secretions or waste, likewise need to be assured of safety. There is also a wider dimension of how to use genetically modified organisms and gene therapy so as to retain the full confidence of the general public.

As with any trial or treatment, the ethical and safety issues for all those involved must be of paramount importance,⁸⁻¹⁴ and regulatory compliance is essential.

This article describes the processes developed in Hammersmith Hospitals Trust since 2001 to undertake gene therapy trials.

Establishing the need for gene therapy trials

Gene therapy trials have been undertaken in Europe, the USA and parts of SE Asia.¹⁵ The UK has a strong basic science background in these areas, and has been involved in trials evaluating gene therapy for single gene disorders.^{16,17,23} The emphasis of current studies in our institution is on the role of gene therapy in treating cancer, cardiovascular disease, and other chronic disorders.

Prior to undertaking the considerable amount of work involved, it was essential to gauge the organizations commitment to such a large programme. The Hospital Trust and partner organizations—Imperial College and the MRC Clinical Sciences Centre—had considerable knowledge and expertise in the relevant science. There was a very strong clinical resource with expertise in diagnosis and treatment of cancer, haematological cancers,

imaging and cardiovascular disease, as well as microbiology, infection control and infectious diseases. Importantly, there was strong NHS Trust support and commitment from departments as diverse as Estates, Pharmacy and Pathology.

It was also recognized early on that specific safety and regulatory issues needed to be considered. An advisory group was convened with a consultant microbiologist (KB) in the Chair.

Legislation and regulations

The UK biotechnology advisory system is complex and interconnecting. Those committees and systems most relevant are the Gene Therapy Advisory Committee (GTAC)¹⁸ and the Health and Safety Executive (HSE) Scientific Advisory Committee on Genetically Modified Organisms (Contained Use)—SACGM (CU),¹⁹ previously the Advisory Committee on Genetic modification (ACGM). Importantly, and introducing improved uniformity across Europe in relation to any clinical trials, the recent introduction of the Clinical Trials Regulations (CTR), mean that, by law, before clinical trials of gene therapy can be conducted in the UK, approval must be obtained from the Medicines and Healthcare Products Regulatory Agency (MHRA).²⁰ The clinical trials directive came into force on 1 May 2004. Most of the provisions are in line with and conform to the principles of good clinical practice, but many make statutory that which was previously regulated only by guidance.^{20,21} Approval from GTAC, the national research ethics committee, which enjoys the same status and functions as the MREC for matters relating to gene therapy, is also essential.

In most cases, a Trust will not be producing the gene therapy agent on site, although this may be the case for academic partners. In these circumstances, systems that conform to Good Manufacturing Practice must be in place. These requirements set out good systems of practice and quality for producing the therapeutic agent, and are reviewed by the MHRA²⁰ and other European agencies.²²

The current UK legislation specifically relating to the contained use of GMMs is the Genetically Modified Organisms (Contained Use) Regulations 2000.²³ Associated with this, the ACGM (now SACGM(CU)), has produced a Compendium of Guidance²⁴ developed to protect humans and the environment from known, potential and unknown hazards of exposure to GMMs. Particular emphasis is placed on a detailed and thorough risk assessment. This includes the management of clinical and laboratory waste and the measures that will be taken to prevent any actual or potential

Table 1 Statutory duties of the employer in relation to the use of genetically modified organisms^{23,24}

To undertake a risk assessment covering human health and safety and environmental safety
To appoint a genetic modification safety committee to advise on risk assessments
To ensure that adequate containment facilities and procedures are in place to control any risks to staff and the environment
To maintain and test equipment at appropriate intervals, and where necessary, to monitor for the presence of viable process organisms outside of containment
To provide adequate training
To formulate and implement local rules
To formulate and implement emergency plans

exposure of people or the environment to the organisms involved. There is also an emphasis on training. More guidance specifically referring to the use of GMMs in clinical settings is expected in the next edition. The duties imposed on the employer by the current guidelines are outlined in Table 1.

As with all other areas of employment, the Health and Safety at Work, etc. Act 1974 (HASAWA), the Management of Health and Safety at Work Regulations 1999 and the Control of Substances Hazardous to Health (COSHH) Regulations 2002 (which includes biological agents)^{25,26} apply to those directly and indirectly involved in gene therapy.

The local regulatory environment

Both the HSE and GTAC take into account the environment in which the study will be conducted. The HSE in particular makes a detailed examination of local safety and containment issues relating to the use of the gene therapy agent. The importance of these local issues should not be underestimated. Compliance with legislation and regulations relating to the containment of GMMs in a clinical rather than laboratory setting is a challenge for any NHS Trust.

Many basic and clinical research laboratories are familiar with the procedures involved and have practices that comply with the various requirements. However, this approach is new to most clinical areas, where it presents particular problems. As with all clinical research, trials also required approval by the local Ethics Committee and had to comply with the Trust's R&D Governance arrangements.

The Genetic Modification Safety Committee

Hammersmith Hospitals Trust created a Genetic Modification Safety Committee (GMSC) to oversee and advise on the conduct of gene therapy and to undertake the specific risk assessments that this work requires. In an NHS Trust clinical setting, this committee is likely to be the Trust's main source of expertise in this field. Its members are therefore well placed to address the implications of this type of activity for the Trust. They can: facilitate the development of good practice, the formation of local rules, and provision of advice on requirements; assist with training, participation in audits of practice and routine management; and assist in the management of accidents and or incidents.

The composition of the GMSC was of necessity broad and reflected the interests of clinicians as well as support services and staff, Trust management and infection control. Membership included those who managed the clinical areas that were principally used for gene therapy, as well as experts in the microbiology of vectors, containment and transmission of micro-organisms in a healthcare environment. The Committee included a medical microbiologist, virologist, infectious disease physician and a safety advisor with GM expertise, as well as senior infection control practitioners, and senior managers from facilities, including waste disposal, portering and domestic services. There were independent staff representatives, the occupational health doctor, a senior pharmacist, a representative of the ethics committee, a representative of the Trust Health and Safety Committee and Trust senior management, as well as representatives of the clinical investigators and the chairs of the GMSCs of partner (e.g. university, MRC) institutions. It was particularly helpful that clinical investigators and specialists in the clinical areas where gene therapy was to be used were involved throughout the process.

In practical terms, day to day guidance was provided by a core working group with appropriate expertise.

Of crucial importance was the willingness of the wider constituency to go through and critically appraise the detailed risk assessments for each trial on a line by line, issue by issue basis.

In addition, a significant amount of time was spent talking to different staff groups in all the areas potentially affected. This allowed people to discuss emotional and ethical as well as scientific reactions, and discuss their concerns and basis for their responses. This approach considerably enhanced

the acceptability of this programme to staff, and in many cases promoted active support of this initiative.

Accountability and communication

The hospital GMSC is a subcommittee of the Trusts Health and Safety Committee. It also interacts with the Trust's clinical governance system via the clinical risk structure, the Infection Control Committee, Environmental management Group and Pathology & Therapies Directorate Health and Safety Committee. Since gene therapy is conducted within a clinical trial environment, the committee also interacted with the Trust's research governance structures, including the Trust's Research and Development office and the relevant Research Ethics Committees.

Key to the conduct of any gene therapy trial within this Trust was acceptance that the local structure must always be able to make decisions based on local issues and take action at any stage following approval from the national bodies (GTAC, MHRA, HSE) about whether a trial can proceed. Thus, in effect, any local concern could result in a gene therapy trial ceasing.

The Biological Safety Officer

A key member of any gene therapy trial team is the Biological Safety Officer (BSO). This individual's function is to provide technical expertise and ensure that appropriate procedures are followed. The specific aspects of this are summarized more clearly in Table 2.

Importantly the person or people involved must have sufficient standing and authority in the organization. In this Trust, each trial has a BSO who is independent of the trial investigating team, but has clinical managerial or scientific expertise in a relevant area. Support is provided by experts on the hospital GMSC.

If the BSO identifies a problem or concern regarding practice relating directly or indirectly to the trial, it is discussed with the Trust safety advisors and the Principal Investigator informed, who must then take remedial action. If the BSO is not satisfied that this is sufficient, he/she will take this to the Chair of the Trust's GMSC and the Clinical Services Director for further action. Clear lines of accountability to the Chief Executive are built into this structure. Records of all meetings and discussions are kept with reporting via clinical and non-clinical structures.

Table 2 The role of the Biological Safety Officer(s)

Ensure that local rules are drawn up and followed
Advise and assist with aspects of training dependant on level of risk
Investigate accidents and incidents
Ensure the safe storage and transport of GMMs
Ensure the appropriate transport and decontamination of GMM containing waste material
Ensure appropriate disinfection procedures are used
Participate in inspections and audits
Advise on methods for testing outside the contained environment
Ensuring appropriate waste disposal procedures are followed
Provide technical support to the GMSC on risk assessment
Ensure all statutory notifications are made to the HSE
Inform and advise on changes to the regulations
Ensure the security of the containment facilities

See reference 24.

Pro-active risk assessment

The local risk assessment process is a key element in deciding whether a trial can proceed in a particular centre and interfaces with the remit of GTAC.

Of the many ways to approach risk assessment in clinical settings,²⁷ a modified semi-structured 'what if' technique was developed. Key to the approach taken was to imagine a 'worst case scenario' or what could go wrong, and then to identify risks at each stage of the three main pathways:

Pathway 1. The gene therapy *agent* pathway addressed how the agent would be produced; how and where it would arrive in the Trust; how and where it would be stored prepared and used; and finally how excess agent and equipment would be inactivated and disposed of.

Pathway 2. The *patient* pathway focused on where the patient would spend time; what would happen to them and how the agent would be administered; how they would have to behave or be treated, how they would be monitored clinically and microbiologically for potential shedding of the agent; how this would affect their treatment and progress; when they could leave confinement, or have visitors, and be discharged; how they would be followed up, and what advice they and their relatives or carers would be given. As well as this, the pathway included what would happen in the case of the need for emergency treatment or unexpected clinical situations as well as environmental emergencies.

Pathway 3. The *waste* pathway asked where waste would be generated; the nature of that waste; how waste containing GMMs or potentially containing GMMs would be identified; and at what stage in the patient pathway it would be produced; how it would be contained and transported; where it would travel; how GMMs would be destroyed in the waste; how waste would be disposed of and how this would be recorded.

At each stage of all these pathways, the specific details of the organism, the work environment, the procedures and practices, unexpected emergencies, the people, occupational health, review and audit arrangements were considered.

The approach taken in this Trust with specific examples is described below.

Potential behaviour of the gene therapy agent

Each agent was assessed, taking into consideration the vector, the modified gene and the resultant combination. Before any individual gene therapy agent was used in clinical trials in humans, there had to be experimental and often animal model evidence to support the local risk assessments. Specifically we looked for published and unpublished evidence of attenuation (a reduction in pathogenicity of the vector). We looked for evidence of the level of expression of any inserted gene and evidence of its effect at the proposed site. For example, an evidence base is developing around the use of herpes and adenovirus vectors in gene therapy for cancer or angiogenesis.^{28–31} Review of relevant papers was requested and discussed.

We required information about possible reversion, recombination and potential expression at unexpected or undesired sites.

Evidence, information and assessment of the risk of shedding (or non-shedding) and the sensitivity of the tests that would be used to monitor this, was sought. Detailed information about known as well as potential effects in all the situations that could occur, including inoculation injury and spillages, was reviewed. This approach addressed the requirement to review the risk to people and the environment from the agent concerned.

The work environment

Risk assessment of the use of GMMs in the clinical environment was more complex. It had to take into account the operation of a busy hospital Trust, with multidisciplinary involvement, often a high staff turnover and unexpected variables such as

emergency clinical situations that could not always be predicted.

'Worst case scenarios' were reviewed, asking what could be done to prevent them. The Committee sought to identify critical control points.

It was also important to address the practical issues of how arrangements would be delivered 24 h a day, 7 days a week, 365 days a year and where necessary required limits to the timing of gene therapy trials.

In HHNT, dedicated facilities were available, including a preparation and storage area with en suite washing and toilet facilities, within the Sir John McMichael Centre, itself a dedicated clinical research and investigation facility. There is limited, monitored access to this centre which is staffed by experienced and fully trained personnel. A major issue for the Trust was that the centre was staffed for 5, not 7, days a week. This was addressed by scheduling therapy administration for early in the week to allow time for screening results to be complete prior to discharge. The trust also developed 'planned' unscheduled use of the infectious diseases ward for patients who were not ready for discharge on the expected day. Staff here were also fully trained in the techniques required, and a detailed hand over procedure including additional training developed. These approaches assessed whether the premises were fit for the intended purpose and skill level of the staff sufficient to effect appropriate containment as described in the regulations.

Procedures and practices

An example of the significant practical problems of commencing gene therapy was the management of waste generated in the clinical area.

Our conventional hospital waste is removed off site before decontamination using microwave treatment or incineration, and then landfill. However, the regulations require GM-waste to be inactivated (decontaminated) by a validated means *before* transport off site. An alternative but very costly approach is to use a GM-registered waste contractor to deal with the clinical waste involved. This was rejected, as the Trust would retain responsibility for safe disposal. There was a choice between validated and controlled chemical disinfection or autoclaving. In practical terms this meant use of a monitored and well-regulated autoclave.

In HHNT, the most suitable autoclaves available were housed in the Microbiology Department, which is internal but quite remote from the gene therapy suite, clinical and ward areas. A separate waste trail was developed with identifying signs,

and internal transport using trained authorized personnel (GM suite nursing staff) and audited critical control points, e.g. leaving the gene therapy suite, reception in the autoclave suite, successful cycle completion. Material containing (or potentially containing) GMMs had to be placed in a sealed leak-proof container robust enough to withstand accidental trauma (dropping/tipping) and suitable for decontamination by a validated means (autoclaving). This presented a significant practical issue. There were no available receptacles for clinical waste (including sharps), that could be sealed, were leak-proof, of a size that could be transported both discretely and safely through the hospital, were acceptable in a ward area and could fit into the autoclave. Custom-sized metal boxes were therefore commissioned. These had to be integrated into the clinical waste trail. An additional problem was the identification of waste containing, or potentially containing, GMMs. Theoretically, not all waste from a clinical area where GMMs are used would present a problem, but the risk assessment identified a potential danger from inappropriate segregation of waste. The most robust policy was therefore to treat all waste from the area concerned in the same way, i.e. as GM waste. While the organisms involved are not believed to pose a hazard to either people or the environment, the precautionary principle was followed since at the time there was not enough evidence to support a reduction in this level of containment.²³

Emergency or unexpected contingencies

Patients who are participating in gene therapy trials have serious underlying illness. It is reasonable to expect that they may require unscheduled or emergency care at some time during the trial period. It was important to consider how this would be managed. For example 'What if patient X developed an acute abdomen on the Friday afternoon of a Bank Holiday week-end?'. This enabled staff to consider appropriate and practical measures. As in the case of HIV-infected subjects,³² gene therapy patients cannot be denied access to appropriate intensive care coronary care, investigative radiology, radiotherapy, etc. because they are, or may be, shedding a potential pathogen. However, neither is it appropriate for them to move freely about the hospital and potentially expose other patients, staff, visitors, and those who may be immunocompromised or pregnant to an agent that may have the potential for unexpected harm. In addition, if gene therapy patients are likely to be discharged when carrying but not shedding the vector i.e. when the patient is

acting as an effective 'biological barrier', procedures need to be in position for scheduled, and unscheduled readmission and policies for management in the event of their needing ambulance transport, or presenting to accident and emergency departments in other hospitals.

A core group of Trust staff had to be trained in the appropriate procedures and there had to be effective out-of-hours cover to advise and deal with unexpected events.

People encountered throughout the process

As well as the patient there were potential interactions with the public, other patients, friends and relatives of the patient, as well as different members of staff at different stages of the treatment. For each group, the possibility of exposure was considered. Policies and practices were introduced to minimize the risk of this happening. Information and training programmes were developed to build up and maintain appropriate awareness and expertise. Detailed training records are kept of the initial GM training received, as well as updates to fulfil the requirement that all staff must be appropriately trained.

Occupational health

The risk assessment for each trial required a procedure and agent specific assessment of possible untoward effects in the event of accidental exposure.

Staff had concerns for their own health and that of their families. A robust and comprehensive occupational health information, screening and monitoring policy was developed to deal with concerns, and to provide mechanisms for monitoring any potential untoward events among staff involved in gene therapy. A staff screening procedure was developed for core trial staff and those more peripherally involved in gene therapy. A staff card, providing a contact number and an indication that the staff were involved in studies, was provided with general and trial-specific training for all staff involved.

Review and audit arrangements

No gene therapy trials were performed in HHT before the infrastructure and support described was in place, so no change in practice or safety can be described. However, vertical and horizontal audits have indicated good practice according to our guidelines. Specifically, review and audit was built into the risk management process.^{14,33} Regular reviews of trials were required. When a

new trial commenced, the management of the first patient was audited. This was cross-checked with the risk assessment, and was a way of reinforcing good practice. There were also regular unit- and trial-based reviews, with monitoring and audit regularly throughout. Auditing of the waste trail, training records and occupational health screening were conducted. Review of the whole activity is also part of the external regulatory process, and there was active involvement from the HSE.

The cost of setting up the infrastructure to start and maintain gene therapy trials within the Trust has been considerable. The most significant cost is staff time. All the committee members contributed. Additionally, a core group spent a lot of time in formal and informal meetings with staff in all the relevant areas in the hospital, as well as developing the risk assessment process and controls assurance guidelines. In order to engage in these activities, the Trust had to take the decision that this was an appropriate cost to bear, also recognizing that it may not be possible to recoup true costs from trial sponsors in all cases.

This paper has focussed on the development of safe systems and an infrastructure within the UK regulatory system. It is important to note that while there is much that is generalizable, there are differences between countries both within Europe and across the world. There is a significant need for more uniformity, particularly within Europe, across this sector. Access to information about the regulatory bodies and their approaches is available via the European Medicines Evaluation Agency. The development of gene therapy products in Europe has been reviewed by Papaluca.³⁴ International links and additional information are also available

from the European Society of Gene Therapy.²² This is a rapidly developing area. New information, recommendations and guidance from national (e.g. SACGM(CU)), and international sources will become available, and will need to be incorporated in to good practice in units involved in this type of work. In addition, many of the principles addressed here are also relevant to broader uses of GMMs in clinical settings, for example in vaccine studies.

Conclusions

The use of GMMs in gene therapy, while likely to be conducted in a discrete area within any healthcare organization, has implications for many areas, services and people involved in an NHS Trust. (Figure 1).

Gene therapy has a positive image among healthcare professionals and the public. This is very important, and reflects the approach taken by all the professional groups involved in developing robust systems, as well as the specific care taken to address the concerns of different individuals and staff groups. Confidence will only be retained if gene therapy is, and continues to be perceived to be, conducted in a responsible and caring way which allows patients with serious and life-threatening diseases access to potentially beneficial therapy, while maintaining the highest possible standards of safety and ethical review. To this end, we have developed a series of standards modelled on the controls assurance standards developed in other areas of health care, such as infection control, in order to provide a framework for us to assess performance in this area (Table 3).

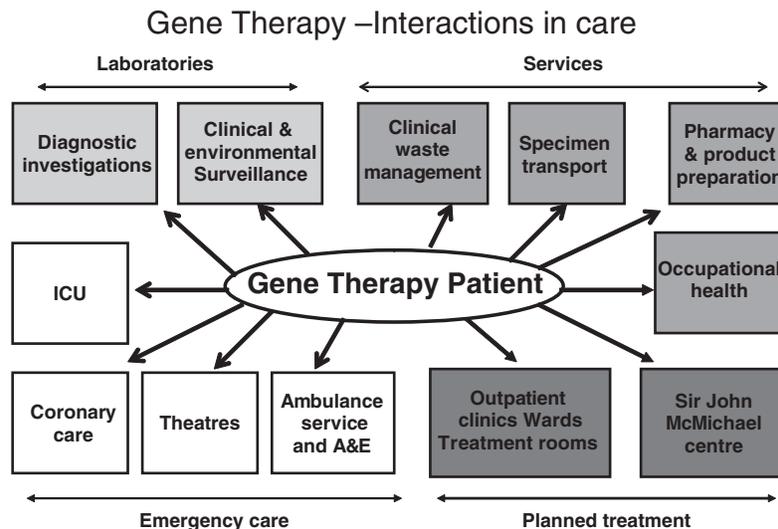


Figure 1. Potential interactions of a gene therapy patient within Hammersmith Hospitals NHS Trust.

Table 3 Proposed standards for conduct of clinical trials involving the use of GMMs

Standard	Components	Verification
1. There should be Board level commitment to gene therapy development in the Trust	<p>Gene therapy is part of the Trust plan.</p> <p>Formal accountability for safety in gene therapy is to the Chief Executive</p> <p>Gene therapy issues are reported through the clinical governance structure</p> <p>Annual report to Trust Board and Risk Management Committee</p> <p>Senior management support for safety issues out of hours</p>	<p>Accountability arrangement chart</p> <p>Minutes</p> <p>GMSC</p> <p>Trust Health and Safety Committee</p> <p>Risk Management Committee</p> <p>Clinical Governance committee</p> <p>Infection Control Committee</p> <p>Trust Board</p> <p>Record of untoward events and reporting</p>
2. There is a GM Safety Committee (GMSC) that endorses all practices involving GMOs, procedures and guidance policies, advice and support on the local implementation, monitors trials and adherence to legislation and guidance	<p>Information is available on appropriate guidance and legislation (AGCM Code of practice)</p> <p>Membership of the GMSC includes:</p> <ul style="list-style-type: none"> Safety advisors with GM expertise Local experts in GM and Gene therapy Microbiologists Virologist Managers of clinical areas involved Waste manager Infection control team Senior clinicians involved Estates and facilities manager Staff representation Safety officer Project biological safety officers <p>The committee should review and approve the risk assessment of all activities before activity commences</p> <p>Review audit of all activities</p> <p>Have agreed terms of reference and reporting channels</p>	<p>Terms of reference</p> <p>Membership list and affiliations</p> <p>Diagram of lines of accountability</p> <p>Minutes</p> <p>Circulation list</p> <p>Annual report</p> <p>Audit reports</p>
3. For each activity or trial there should be a properly constituted investigative team	<p>Each study team constitutes:</p> <ul style="list-style-type: none"> Principal investigator (PI) Trial members Biological Safety Officer(s) <p>The PI is responsible for the management of the trial.</p> <p>PI is responsible for safety management of all areas of activity.</p> <p>PI is responsible for ensuring there is an appropriate level of training of all staff involved in each activity or trial.</p> <p>PI is responsible for carrying out a full risk assessment of all procedures involved in each activity or trial.</p> <p>PI is responsible for ensuring all staff involved have occupational health screening and advice.</p>	<p>Copies of Trust GM and Gene therapy policies</p> <p>Risk assessments</p>

(Continued)

Table 3 Continued

Standard	Components	Verification
4. Written policies, procedures and guidance for management of work with GMOs are implemented and reflect relevant legislation and published professional guidelines	<p>PI liaises and takes advice from safety advisor and the chair of the Gene therapy and GM safety committee in all matters relating to safety.</p> <p>Policies, procedures and guidance should be approved by the GMSC. Each department involved in work with GMOs should have a copy of the approved policies, procedures and guidelines pertinent to its activities.</p> <p>Policies should be in place including:</p> <ul style="list-style-type: none"> Risk assessment and approval procedures Preparation, storage and handling of GT agents Administration of GT products Maintenance of premises and accommodation for GT Disposal of GM waste Transport of specimens Staff protection Reporting of incidents Emergency procedures Unscheduled investigation and treatment Management of occupational exposure to GT products Decontamination of ward/ environment and devices <p>Policies should be clearly marked with a review date</p>	Copies of policies
5. A comprehensive annual report on all activity is produced by the GMSC and presented to the HHT SC reviewed by the Risk Management Committee and presented to the Board	<p>Report should include:</p> <ul style="list-style-type: none"> Update on all projects Number enrolled and completed Audit of project <ul style="list-style-type: none"> 1st patient + quarterly Extended admissions Untoward events Impact on resources Incidents: <ul style="list-style-type: none"> Investigations Reports Measures to prevent recurrence Education and training undertaken External review <ul style="list-style-type: none"> HSE inspections and visit reports 	Copy of reports
6. The GMSC + BSOs have access to up to date legislation and guidance relevant to gene therapy and GM	<p>Access to:</p> <ul style="list-style-type: none"> ACGM Code of Practice HSE newsletters Web access 	<p>Evidence of use of:</p> <ul style="list-style-type: none"> Library Internet Safety Office/Advisor

(Continued)

Table 3 Continued

Standard	Components	Verification
7. All staff directly and peripherally involved in gene therapy are trained to an appropriate level	<p>PI and investigative team have received general and specific study orientated GM training.</p> <p>Support teams have received general, project and area specific GM training.</p> <p>Staff regularly but peripherally involved have received general GM training.</p> <p>There should be regular updates to training.</p>	<p>Training programmes</p> <p>Training records</p>
8. The system for GMO safety is monitored and reviewed by Management and the Board in order to ensure the Trust's compliance with legislation	<p>The Chief Executive and Board should monitor all aspects of the use of GMOs on Trust premises</p> <p>Accountability arrangements</p> <p>Processes including:</p> <ul style="list-style-type: none"> Risk management Capability Internal audit findings <p>The GMSC will review detailed issues surrounding the use of GMMs within the Trust. The Trust Safety Committee, Clinical Risk Committee, Audit Committee and Clinical Governance Committees, will review this. They will play a significant role in monitoring and reviewing the system as a basis of what should be presented to and dealt with by the Trust Board.</p>	<p>Internal audit reports</p> <p>Audit Committee minutes</p> <p>Infection Control Committee minutes</p> <p>Risk Management Committee minutes</p> <p>Clinical Governance Committee minutes</p> <p>Health and Safety Committee minutes</p> <p>Annual report to Trust Board</p>
9. The internal audit function in conjunction with the GMSC and Health and Safety Committee carries out periodic audit to provide assurances to the Board that a suitable system for working with GMSC, including risk assessment and management, that conforms to legislation and national guidance is in place and working properly	<p>Internal auditors in collaboration with GMSC should periodically verify that a suitable and effective system of internal control exists with respect to work with GMOs. The level of internal audit should be carried out based on risk, which will be determined principally by reference to assurances given by the GMSC and PIs.</p> <p>Reports should be presented to the Audit Committee and copied to the Risk Management Committee, Infection Control Committee and other relevant board sub-committees (e.g. Clinical Governance).</p> <p>An annual internal audit statement should be presented to the Chief Executive where the system in place for work with GMOs has been audited. This should be referred to in the statement.</p>	<p>Reports</p> <p>Internal audit</p> <p>Minutes Audit or GMCS committee</p> <p>Risk management committee</p> <p>Infection control committee</p>

(Continued)

Table 3 Continued

Standard	Components	Verification
10. Use of GMMs in clinical trials should comply with good research governance with in the Trust and partner institutions	There should be external review by GTAC There should be ethical review There should be appropriate indemnity arrangements There should be appropriate funding arrangements There should be a formal research contract	GTAC approval Ethics approval Trust research governance records

Multidisciplinary staff involvement in developing these procedures has been crucial. Without an informed, responsible and responsive workforce, translation of the basic science of gene therapy into the clinical arena would not have occurred.

None of the individual steps required is of itself intrinsically difficult, but to deliver the whole package well, a hospital Trust requires a significant ideological, organizational and financial commitment. Trusts should not undertake this lightly. It is appropriate for regulatory bodies involved in this area to expect this level of commitment from any trust that proposes to develop a programme of clinical gene therapy or use GMMs in any clinical setting.

Acknowledgements

We thank Dr Monica Preuss, GTAC, for helpful comments on this manuscript and Dr Paul Logan, HSE, for helpful advice, both during the project, and in the manuscript preparation.

References

- Rubanyi GM. The future of human gene therapy. *Mol Aspects Med* 2001; **22**:113–42.
- St George JA. Gene therapy progress and prospects: adenoviral vectors. *Gene Ther* 2003; **10**:1135–41.
- Tsokos GC, Tsokos M. The TRAIL to arthritis. *J Clin Invest* 2003; **112**:1315–17.
- Dobbelstein M. Viruses in therapy—royal road or dead end? *Virus Res* 2003; **92**:219–21.
- Vile R, Ando D, Kim D. The oncolytic virotherapy treatment platform for cancer: unique biological and biosafety points to consider. *Cancer Gene Ther* 2002; **9**:1062–7.
- Kaiser J. Gene therapy. RAC hears a plea for resuming trials, despite cancer risk. *Science* 2003; **299**:991.
- Kaiser J. Gene therapy. RAC's advice: proceed with caution. *Science* 2002; **298**:2113–15.
- Lai CM, Lai YK, Rakoczy PE. Adenovirus and adeno-associated virus vectors. *DNA Cell Biol* 2002; **21**:895–913.
- Evans ME, Lesnaw JA. Infection control for gene therapy: a busy physician's primer. *Clin Infect Dis* 2002; **35**:597–605.
- Graffunder EM, Venezia RA. Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials. *J Antimicrob Chemother* 2002; **49**:999–1005.
- Bridges CB, Kuehnert MJ, Hall CB. Transmission of influenza: implications for control in health care settings. *Clin Infect Dis* 2003; **37**:1094–101.
- Knorr D. Human gene therapy: ensuring progress in the next millennium. *Natl Forum* 1999; **79**:31–4.
- Seymour LW. Trial and error. *Lancet* 2003; **361**:1568.
- Sullivan R. United Kingdom research governance strategy: reforming clinical research and development in England. *Br Med J* 2004; **328**:49–50.
- Dube ID, Cournoyer D. Gene therapy: here to stay. *CMAJ* 1995; **152**:1605–13.
- Griesenbach U, Geddes DM, Alton EW. Update on gene therapy for cystic fibrosis. *Curr Opin Mol Ther* 2003; **5**:489–94.
- Flotte TR. Gene therapy for cystic fibrosis. *Curr Opin Mol Ther* 1999; **1**:510–16.
- Gene Therapy Advisory Committee, 2004. [www.doh.gov.uk/genetics/gtac].
- Scientific Advisory Committee on Genetically Modified Organisms (Contained Use), 2004. [http://www.hse.gov.uk/aboutus/meetings/sacgmcu/index.htm].
- Medicines and Healthcare Products Regulatory Agency, 2004. [http://www.mhra.gov.uk].
- Clinical Trials Directive (2001/20/EC), 2004. [http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/clinicaldir.htm].
- The European Society of Gene Therapy, 2004. [www.abedi.se/esgt/index.html].
- Genetically Modified Organisms (Contained Use) Regulations 2000. London, HMSO, 2000.
- Health and Safety Executive, Advisory Committee on Genetic Modification Compendium of Guidance 2002. London, HMSO, 2002.
- Health and Safety at Work Act 1974. London, HMSO, 1974.
- Control of Substances Hazardous to Health (COSHH) Regulations 1999. London, HMSO, 1999.
- Roberts G. Risk management methods. In: *Risk Management in Healthcare*, 2nd edn. London, Witherby, 2002:81–166.

28. Kubo H, Gardner TA, Wada Y, Koeneman KS, Gotoh A, Yang L, Kao C, Lim SD, Amin MB, Yang H, Black ME, Matsubara S, Nakagawa M, Gillenwater JY, Zhou HE, Chung LW. Phase I dose escalation clinical trial of adenovirus vector carrying osteocalcin promoter-driven herpes simplex virus thymidine kinase in localized and metastatic hormone-refractory prostate cancer. *Hum Gene Ther* 2003; **14**:227–41.
29. Hedman M, Hartikainen J, Syvanne M, et al. Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene transfer in the prevention of postangioplasty and in-stent restenosis and in the treatment of chronic myocardial ischemia: phase II results of the Kuopio Angiogenesis Trial (KAT). *Circulation* 2003; **107**:2677–83.
30. Burton EA, Fink DJ, Glorioso JC. Gene delivery using herpes simplex virus vectors. *DNA Cell Biol* 2002; **21**:915–36.
31. Khan TA, Sellke FW, Laham RJ. Gene therapy progress and prospects: therapeutic angiogenesis for limb and myocardial ischemia. *Gene Ther* 2003; **10**:285–91.
32. Bhagwanjee S, Muckart DJ, Jeena PM, Moodley P. Does HIV status influence the outcome of patients admitted to a surgical intensive care unit? A prospective double blind study. *Br Med J* 1997; **314**:1077–81.
33. Agnihotri N, Bhasin DK, Vohra H, Ray P, Singh K, Ganguly NK. Characterization of lymphocytic subsets and cytokine production in gastric biopsy samples from Helicobacter pylori patients. *Scand J Gastroenterol* 1998; **33**:704–9.
34. Papaluca Amati M, Pignatti F, Nolte A, Amerasinghe N, Gustafsson D, Moulon I, Le Courtis P. EMEA and Gene Therapy Medicinal Products Development in the European Union. *J Biomed Biotechnol* 2003; **2003**:3–8.