Risk Assessment in Clinical Trials

Introduction

This research aims to investigate how gene therapy researchers take account of considerations of risk when making decisions about the design and conduct of gene therapy clinical trials.

The questionnaire will take approximately 10-15 minutes to complete. The questions have been divided into the following sections, which will appear on separate pages.

Part A: demographic details (12 questions)
Part B: decisions about initiating a clinical trial (8 questions, 7 parts each)
Part C: general attitudes to research involving human subjects (5 questions)
Part D: attitudes to research involving human subjects based on personal experience (4 questions)
Part E: additional comments (optional; 1 question)

Even though you may not have been involved in trials analogous to the specific hypothetical scenarios described in Part B, we would value your judgments regarding risk-benefit assessment in these scenarios, based on your involvement and experience in research directed towards treating disease.

Thank you for giving your time to participate in our research. We greatly appreciate your thoughtful responses.

A) Demographic details

Please select the most appropriate answer.

(1) Please indicate your gender

☐ Female ☐ Male

(2) Please indicate your age

☐ 21-30 years
☐ 31-40 years
☐ 41-50 years
☐ 51-60 years
☐ Over 60 years

(3) In which country do you conduct your research?

If your research is part of a multi-centre study, please select the country in which the centre you conduct research at is based.

☐ Australia	☐ Czech Republic	☐ Germany	☐ Mexico	☐ Russia	☐ Switzerland
☐ Austria	☐ Denmark	☐ Ireland	☐ Netherlands	☐ Singapore	☐ Taiwan
☐ Belgium	☐ Egypt	☐ Israel	☐ New Zealand	☐ South Korea	☐ United Kingdom
☐ Canada	☐ Finland	☐ Italy	☐ Norway	☐ Spain	☐ United States
☐ China	☐ France	☐ Japan	☐ Poland	☐ Sweden	☐ Other (*please specify*)

(4) Have you been involved in a clinical trial in any way?

☐ Yes ☐ No

(5) What are/were your role(s) in a current or completed clinical trial?

Select more than one description if applicable.

☐ Generated preclinical data ☐ Vector production ☐ Consent ☐ Not applicable

☐ Trial design ☐ Consent ☐ Analysis of data ☐ Other (*please specify*)

☐ Recruitment of subjects ☐ Clinical treatment or management ☐ Manuscript preparation

(6) What is the research setting for the preclinical research?

Select more than one if applicable

☐ Hospital ☐ University ☐ Independent research institute ☐ Other (*please specify*)

(7) Does the target population for your research include children?

☐ Yes ☐ No

(8) Are you involved in the clinical care of children, independent of any involvement you may have had in a clinical trial?

☐ Yes ☐ No ☐ Not applicable

(9) Are you a scientist, clinician or both?

☐ Scientist ☐ Clinician ☐ Both scientist and clinician

(10) If you answered "both clinician and scientist" in Question 9, please indicate approximately what percentage of your time is spent conducting research and what percentage of your time is spent in the clinic.

☐ 10% research, 90% clinic ☐ 40% research, 60% clinic ☐ 70% research, 30% clinic

☐ 20% research, 80% clinic ☐ 50% research, 50% clinic ☐ 80% research, 20% clinic

☐ 30% research, 70% clinic ☐ 60% research, 40% clinic ☐ 90% research, 10% clinic

(11) Please select the most applicable descriptions of your field of research

Select more than one description if applicable

☐ Cancer/ oncology	☐ Respiratory	☐ Neurology	☐ Ophthalmic	☐ Other (*please specify*)
☐ Metabolic	☐ Haematology	☐ Neurodegenerative	☐ Infectious	
☐ Cardiovascular	☐ Immunology	☐ Musculo-skeletal	☐ Monogenic genetic disease	

(12) How many years have you been working in this field?

☐ 1-5 years	☐ 16-20 years
☐ 5-10 years	☐ 21-25 years
☐ 11-15 years	☐ Over 25 years

B) Decisions about initiating a clinical trial

(1) Do you think it would be appropriate to recruit subjects to a phase I trial* on the basis of

a statistically powered study demonstrating therapeutic efficacy in relevant primary human cells in culture AND evidence of safety in a validated cell culture assay

in the following context?

	Strongly agree	Agree	Disagree	Strongly disagree
No available treatment, presents at birth or soon after, death in infancy	☐	☐	☐	☐
No available treatment, rapidly progressive, poor quality of life (QoL), death in childhood/adolescence	☐	☐	☐	☐
No available treatment, slowly progressive, poor QoL during final 10 years, death in early adulthood	☐	☐	☐	☐
No available treatment, QoL acceptable until end-stage, life expectancy reduced by 20 years	☐	☐	☐	☐
Disease can be cured by allogeneic bone marrow transplantation, but prior myeloablation is required and transplant may be associated with acute and chronic graft-versus-host disease and other serious and secondary effects e.g. malignancy. Survival rate is 65% at 10 years. QoL in survivors is reduced but generally regarded as acceptable.	☐	☐	☐	☐
Disease can be controlled by regular blood transfusions, which over time may lead to iron overload and cardiac failure. Life expectancy and QoL are reduced, although QoL is considered acceptable in most cases.	☐	☐	☐	☐
Disease can be controlled by diet, but compliance is poor and low grade neurocognitive damage is likely. Life expectancy is normal in most patients and QoL is generally acceptable.	☐	☐	☐	☐

**A phase I trial is the first stage of testing in human subjects and is designed to assess the safety of a new therapy.*

(2) Do you think it would be appropriate to recruit subjects to a phase I trial* on the basis of

> **a statistically powered study demonstrating therapeutic efficacy in relevant primary human cells in culture AND evidence of safety in a validated cell culture assay, if a knock-out mouse model is expected to be generated within two years**

in the following context?

	Strongly agree	Agree	Disagree	Strongly disagree
No available treatment, presents at birth or soon after, death in infancy	☐	☐	☐	☐
No available treatment, rapidly progressive, poor quality of life (QoL), death in childhood/adolescence	☐	☐	☐	☐
No available treatment, slowly progressive, poor QoL during final 10 years, death in early adulthood	☐	☐	☐	☐
No available treatment, QoL acceptable until end-stage, life expectancy reduced by 20 years	☐	☐	☐	☐
Disease can be cured by allogeneic bone marrow transplantation, but prior myeloablation is required and transplant may be associated with acute and chronic graft-versus-host disease and other serious and secondary effects e.g. malignancy. Survival rate is 65% at 10 years. QoL in survivors is reduced but generally regarded as acceptable.	☐	☐	☐	☐
Disease can be controlled by regular blood transfusions, which over time may lead to iron overload and cardiac failure. Life expectancy and QoL are reduced, although QoL is considered acceptable in most cases.	☐	☐	☐	☐
Disease can be controlled by diet, but compliance is poor and low grade neurocognitive damage is likely. Life expectancy is normal in most patients and QoL is generally acceptable.	☐	☐	☐	☐

**A phase I trial is the first stage of testing in human subjects and is designed to assess the safety of a new therapy.*

(3) Do you think it would be appropriate to recruit subjects to a phase I trial* on the basis of

a statistically powered study demonstrating safety and therapeutic efficacy, in correcting a mouse phenotype with no evidence of toxicity or adverse events in long term follow up, using a mouse model where the phenotype is the same as the human disease (no large animal model available)

in the following context?

	Strongly agree	Agree	Disagree	Strongly disagree
No available treatment, presents at birth or soon after, death in infancy	☐	☐	☐	☐
No available treatment, rapidly progressive, poor quality of life (QoL), death in childhood/adolescence	☐	☐	☐	☐
No available treatment, slowly progressive, poor QoL during final 10 years, death in early adulthood	☐	☐	☐	☐
No available treatment, QoL acceptable until end-stage, life expectancy reduced by 20 years	☐	☐	☐	☐
Disease can be cured by allogeneic bone marrow transplantation, but prior myeloablation is required and transplant may be associated with acute and chronic graft-versus-host disease and other serious and secondary effects e.g. malignancy. Survival rate is 65% at 10 years. QoL in survivors is reduced but generally regarded as acceptable.	☐	☐	☐	☐
Disease can be controlled by regular blood transfusions, which over time may lead to iron overload and cardiac failure. Life expectancy and QoL are reduced, although QoL is considered acceptable in most cases.	☐	☐	☐	☐
Disease can be controlled by diet, but compliance is poor and low grade neurocognitive damage is likely. Life expectancy is normal in most patients and QoL is generally acceptable.	☐	☐	☐	☐

**A phase I trial is the first stage of testing in human subjects and is designed to assess the safety of a new therapy.*

(4) Do you think it would be appropriate to recruit subjects to a phase I trial* on the basis of

a statistically powered study demonstrating safety and therapeutic efficacy, in correcting a mouse phenotype with no evidence of toxicity or adverse events in long term follow-up, using a mouse model that involves the same gene but where the phenotype differs from the human disease (no large animal model available)

in the following context?

	Strongly agree	Agree	Disagree	Strongly disagree
No available treatment, presents at birth or soon after, death in infancy	☐	☐	☐	☐
No available treatment, rapidly progressive, poor quality of life (QoL), death in childhood/adolescence	☐	☐	☐	☐
No available treatment, slowly progressive, poor QoL during final 10 years, death in early adulthood	☐	☐	☐	☐
No available treatment, QoL acceptable until end-stage, life expectancy reduced by 20 years	☐	☐	☐	☐
Disease can be cured by allogeneic bone marrow transplantation, but prior myeloablation is required and transplant may be associated with acute and chronic graft-versus-host disease and other serious and secondary effects e.g. malignancy. Survival rate is 65% at 10 years. QoL in survivors is reduced but generally regarded as acceptable.	☐	☐	☐	☐
Disease can be controlled by regular blood transfusions, which over time may lead to iron overload and cardiac failure. Life expectancy and QoL are reduced, although QoL is considered acceptable in most cases.	☐	☐	☐	☐
Disease can be controlled by diet, but compliance is poor and low grade neurocognitive damage is likely. Life expectancy is normal in most patients and QoL is generally acceptable.	☐	☐	☐	☐

**A phase I trial is the first stage of testing in human subjects and is designed to assess the safety of a new therapy.*

(5) Do you think it would be appropriate to recruit subjects to a phase I trial* on the basis of

> **a statistically powered study demonstrating safety and therapeutic efficacy, in correcting a mouse phenotype with no adverse events, using a mouse model where the phenotype is the same as the human disease AND when a large animal model is available but a large animal study would delay trial initiation by 3 years**

in the following context?

	Strongly agree	Agree	Disagree	Strongly disagree
No available treatment, presents at birth or soon after, death in infancy	☐	☐	☐	☐
No available treatment, rapidly progressive, poor quality of life (QoL), death in childhood/adolescence	☐	☐	☐	☐
No available treatment, slowly progressive, poor QoL during final 10 years, death in early adulthood	☐	☐	☐	☐
No available treatment, QoL acceptable until end-stage, life expectancy reduced by 20 years	☐	☐	☐	☐
Disease can be cured by allogeneic bone marrow transplantation, but prior myeloablation is required and transplant may be associated with acute and chronic graft-versus-host disease and other serious and secondary effects e.g. malignancy. Survival rate is 65% at 10 years. QoL in survivors is reduced but generally regarded as acceptable.	☐	☐	☐	☐
Disease can be controlled by regular blood transfusions, which over time may lead to iron overload and cardiac failure. Life expectancy and QoL are reduced, although QoL is considered acceptable in most cases.	☐	☐	☐	☐
Disease can be controlled by diet, but compliance is poor and low grade neurocognitive damage is likely. Life expectancy is normal in most patients and QoL is generally acceptable.	☐	☐	☐	☐

**A phase I trial is the first stage of testing in human subjects and is designed to assess the safety of a new therapy.*

(6) Do you think it would be appropriate to recruit subjects to a phase I trial* on the basis of

> **a statistically powered study demonstrating safety and therapeutic efficacy in a large animal model, in correcting a disease phenotype that is the same as the human disease and with no adverse events in long term follow-up**

in the following context?

	Strongly agree	Agree	Disagree	Strongly disagree
No available treatment, presents at birth or soon after, death in infancy	☐	☐	☐	☐
No available treatment, rapidly progressive, poor quality of life (QoL), death in childhood/adolescence	☐	☐	☐	☐
No available treatment, slowly progressive, poor QoL during final 10 years, death in early adulthood	☐	☐	☐	☐
No available treatment, QoL acceptable until end-stage, life expectancy reduced by 20 years	☐	☐	☐	☐
Disease can be cured by allogeneic bone marrow transplantation, but prior myeloablation is required and transplant may be associated with acute and chronic graft-versus-host disease and other serious and secondary effects e.g. malignancy. Survival rate is 65% at 10 years. QoL in survivors is reduced but generally regarded as acceptable.	☐	☐	☐	☐
Disease can be controlled by regular blood transfusions, which over time may lead to iron overload and cardiac failure. Life expectancy and QoL are reduced, although QoL is considered acceptable in most cases.	☐	☐	☐	☐
Disease can be controlled by diet, but compliance is poor and low grade neurocognitive damage is likely. Life expectancy is normal in most patients and QoL is generally acceptable.	☐	☐	☐	☐

**A phase I trial is the first stage of testing in human subjects and is designed to assess the safety of a new therapy.*

(7) Do you think it would be appropriate to recruit subjects to a phase I trial* on the basis of

convincing preclinical safety and efficacy data in a mouse model AND data from a phase I trial targeting a different disease of the same target tissue, which used the same technological intervention and demonstrated therapeutic efficacy and no adverse events

in the following context?

	Strongly agree	Agree	Disagree	Strongly disagree
No available treatment, presents at birth or soon after, death in infancy	☐	☐	☐	☐
No available treatment, rapidly progressive, poor quality of life (QoL), death in childhood/adolescence	☐	☐	☐	☐
No available treatment, slowly progressive, poor QoL during final 10 years, death in early adulthood	☐	☐	☐	☐
No available treatment, QoL acceptable until end-stage, life expectancy reduced by 20 years	☐	☐	☐	☐
Disease can be cured by allogeneic bone marrow transplantation, but prior myeloablation is required and transplant may be associated with acute and chronic graft-versus-host disease and other serious and secondary effects e.g. malignancy. Survival rate is 65% at 10 years. QoL in survivors is reduced but generally regarded as acceptable.	☐	☐	☐	☐
Disease can be controlled by regular blood transfusions, which over time may lead to iron overload and cardiac failure. Life expectancy and QoL are reduced, although QoL is considered acceptable in most cases.	☐	☐	☐	☐
Disease can be controlled by diet, but compliance is poor and low grade neurocognitive damage is likely. Life expectancy is normal in most patients and QoL is generally acceptable.	☐	☐	☐	☐

**A phase I trial is the first stage of testing in human subjects and is designed to assess the safety of a new therapy.*

(8) Do you think it would be appropriate to recruit subjects to a phase I trial* on the basis of

convincing preclinical safety and efficacy data in a mouse model AND data from a phase I trial targeting a different disease of the same target tissue, which used the same technological intervention and demonstrated therapeutic efficacy and a low frequency of serious and life-threatening adverse events (e.g. less than 10%)

in the following context?

	Strongly agree	Agree	Disagree	Strongly disagree
No available treatment, presents at birth or soon after, death in infancy	☐	☐	☐	☐
No available treatment, rapidly progressive, poor quality of life (QoL), death in childhood/adolescence	☐	☐	☐	☐
No available treatment, slowly progressive, poor QoL during final 10 years, death in early adulthood	☐	☐	☐	☐
No available treatment, QoL acceptable until end-stage, life expectancy reduced by 20 years	☐	☐	☐	☐
Disease can be cured by allogeneic bone marrow transplantation, but prior myeloablation is required and transplant may be associated with acute and chronic graft-versus-host disease and other serious and secondary effects e.g. malignancy. Survival rate is 65% at 10 years. QoL in survivors is reduced but generally regarded as acceptable.	☐	☐	☐	☐
Disease can be controlled by regular blood transfusions, which over time may lead to iron overload and cardiac failure. Life expectancy and QoL are reduced, although QoL is considered acceptable in most cases.	☐	☐	☐	☐
Disease can be controlled by diet, but compliance is poor and low grade neurocognitive damage is likely. Life expectancy is normal in most patients and QoL is generally acceptable.	☐	☐	☐	☐

**A phase I trial is the first stage of testing in human subjects and is designed to assess the safety of a new therapy.*

C) General attitudes to research involving human subjects

To what extent do you agree or disagree with the following statements?

(1) In the context of a severe disease when treatment does not exist, it is **acceptable** to proceed to clinical trials in the absence of toxicological data.

Strongly agree	Agree	Disagree	Strongly disagree
☐	☐	☐	☐

(2) The absence of adverse events in small animal models does **not** enable meaningful predictions to be made about long-term safety in humans.

Strongly agree	Agree	Disagree	Strongly disagree
☐	☐	☐	☐

(3) It is more important to have a greater prospect of benefit to participants in trials involving children than in trials involving adults.

Strongly agree	Agree	Disagree	Strongly disagree
☐	☐	☐	☐

(4) In the context of a progressive disease, it is preferable for novel therapeutic modalities with uncertain risks and benefits to be trialled initially on patients with **advanced disease** (where the patient may have 'less to lose' but also less likelihood of benefit), rather than on patients with **early disease stage** (where the patient may have a greater likelihood of benefit but also have more to lose), even when this is likely to compromise the capacity of a trial to assess efficacy.

Strongly agree	Agree	Disagree	Strongly disagree
☐	☐	☐	☐

(5) In the context of a severe disease with rapid clinical course when treatment options have been exhausted or there is no established treatment, it may be acceptable to proceed to the clinic on the basis of a statistically powered animal study, in which endpoint measures of therapeutic benefit fall just short of clinical significance (i.e. $p \geq 0.05$).

Strongly agree	Agree	Disagree	Strongly disagree
☐	☐	☐	☐

D) Attitudes to research involving human subjects based on personal experience

Please answer the following questions based on your own experience.

(1) When a decision is made about commencing a trial, to what extent is the potential for adverse events to have a negative effect on **public support and trust** a relevant consideration?

Completely irrelevant	Somewhat irrelevant	Somewhat relevant	Very relevant	Not applicable
☐	☐	☐	☐	☐

(2) When a decision is made about commencing a trial, to what extent is the potential for adverse events to have a negative effect on **your field of research** a relevant consideration?

For example, by affecting funding, the decisions of funding bodies, or the decisions of other researchers

Completely irrelevant	Somewhat irrelevant	Somewhat relevant	Very relevant	Not applicable
☐	☐	☐	☐	☐

(3) Has your own **personal** decision-making about clinical trials ever been affected in any way by a report of an adverse event in a trial in your field?

For example, has your enthusiasm for developing, initiating or participating in a clinical trial been affected by adverse events occurring in another trial?

Completely irrelevant	Somewhat irrelevant	Somewhat relevant	Very relevant	Not applicable
☐	☐	☐	☐	☐

(4) Please give reasons for your response.

Optional, but any brief comments would be greatly appreciated.

E) Additional comments

Are there any additional comments or views that you would like to express?

This question has been included to give you an opportunity to express any additional comments, views or concerns that you may have about decision-making in clinical research, including comments that might arise from dissatisfaction with the present questionnaire.

*It is **optional**, but we would greatly appreciate any comments you may have.*