HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Completing a Non-~~Technical~~ technical Project Summary for a Project under Scientific Animal Protection Legislation

AUT-G0103-3.1
~~**26 MAY 2014**~~

CONTENTS

1 SCOPE

This guidance relates to the completion of a non-technical project summary form for project applications submitted for authorisation under Directive 2010/63/EU (the Directive) and S.I. No. 543 of 2012, as amended by S.I. No. 434 of 2013 and S.I. No. 174 of 2014 (hereafter referred to as the S.I.). This form must be submitted to the HPRA in relation to project applications involving animals used for scientific purposes, including projects relating to regulatory and diagnostic testing of chemicals or biological substances, as well as for educational purposes.

2 INTRODUCTION

The protection of animals used for scientific procedures is governed by Directive 2010/63/EU which was transposed into Irish law by S.I. No. 543 of 2012. Article 43 of Directive 2010/63/EU and Regulation 33 of S.I. No. 543 of 2012 describe the content of the non-technical project summary. A non-technical project summary (NTPS) is a mandatory requirement for all project~~s~~ applications submitted to the HPRA under Regulation 25 (2) of the S.I. An application for a project will not be validated for assessment by the HPRA until the NTPS is submitted.

The NTPS is intended to provide information to the public about the projects and procedures being conducted, including how compliance with the 3R principles of replacement, reduction and refinement is being assured. The NTPS must be written in a clear and concise manner using plain language understandable to a non-expert where possible i.e. succinct and avoiding the use of highly technical terms and descriptions. Aside from section A of the NTPS form (which will not be published), the NTPS must **not** contain the names and addresses of any person or establishment, or any information relating to the intellectual property of the project work involved in conducting the project.

The NTPS is to be completed by the project manager or deputy project manager (if applicable) for the project authorisation. In the case of an amendment to an authorised project, the relevant NTPS must also be updated. Please see Appendix II for an illustrative example of a completed NTPS as developed by the EU Commission.

The HPRA is obliged to ensure that following authorisation of a project, the NTPS is published, subject to safeguarding intellectual property rights and confidential information. The HPRA therefore depends on the applicant to ensure that only information that is suitable for publication is included in the NTPS. It should be noted that the NTPS will remain accessible to the public for a period of three years after the expiry of the project authorisation.

3 APPLICATIONS FOR A NON-TECHNICAL PROJECT SUMMARY

3.1 Section A - Applicant details

Enter the details of the project manager ~~and deputy project manager (if applicable) information~~ in this part of the form. This section is confidential and will not be made available to the public. The purpose of identifying the primary establishment is to ensure internal HPRA traceability and to facilitate any inspections that may be required by the HPRA.

~~The HPRA will use the applicant details provided in the project application should a need to revise or amend the NTPS arise. The HPRA will also use these details to notify its decision to publish the NTPS to the establishment concerned.~~

An internal identification number ~~(HPRA case number)~~ will appear in the publicly available report, but is used only to facilitate tracking internally within the HPRA. This identification number will change should an update of the ~~NTSP~~ NTPS be required.

3.2 Section B - Project information

~~3.2~~

3.2.1 Project title

The title of the project should be summarised in ~~less~~ fewer than 3~~5~~00 characters. Where the project is being conducted to satisfy regulatory requirements, the word 'regulatory' should be included as the first word in the project title. In all other cases the word 'research' should be included as the first word in the title. Following this, the title should capture the project objective or study aim. It is also required to include the species of test animals in the title. High-level and easily understood terms should be used e.g. cardio-vascular, cancer (rather than oncology), educational, toxicology etc.

3.2.2 Species and number of animals

The species and approximate number of animals expected to be used in the project~~study~~ must be provided.

~~3.2.2~~3.2.3 Expected duration of project work

The expected project duration should be specified in months. The maximum period a project can run is 60 months (5 years). If the project runs over the 5-year limit, it will be necessary to submit a renewal application.

~~3.2.3~~3.2.4 Project keywords

List up to ~~five~~ ten keywords. The purpose of this section is to facilitate searching. One of the~~e~~ keywords should include the species of animals under study.

3.3 Section C - Project purpose~~Section C – Project purpose~~

This section relates to information that the HPRA is required to collect for statistical and reporting purposes on the use of animals in procedures.

Choose the most relevant project category from the category types outlined in the sections below and using Appendix I. Please choose only one main heading and provide further details ~~on~~in the associated sub-fields, if required. These categories have been established by the EU Commission and are not open to change by the HPRA. Note that only one project purpose can be selected for each project.

3.3.1 Basic research

Basic research includes studies of a fundamental nature including physiology. It also includes:
- ~~Studies~~ studies that are designed to add knowledge about normal and abnormal structure,
- ~~Functioning~~ functioning and behaviour of living organisms and environment as well as fundamental studies in toxicology,
- ~~Investigations~~ investigations and analyses that are focused on a better or fuller understanding of a subject, phenomenon, or a basic law of nature instead of on a specific practical application of the results and,
- ~~Studies~~ studies relating to the creation of a new genetically altered animal line.

3.3.2 Translational and applied research

This describes the translational and applied research, including discovery toxicology and investigations to prepare for the regulatory submission and method development.

3.3.3 Regulatory use and routine production by type

This describes the use of animals in procedures performed with a view to satisfying legal requirements for producing, placing and maintaining products/substances on the market, including safety and risk assessments for food and feed.

This category includes tests carried out on products/substances for which no regulatory submission is ultimately made. These tests would have been included in a regulatory submission had a submission occurred (i.e. tests performed on those products/substances that fail to reach the end of the development process).

The category also includes tests on animals used in the manufacturing process of products if the manufacturing process requires regulatory approval (e.g. include animals used in the manufacturing of serum-based medicinal products within this category).

The efficacy testing during the development of new medicinal products is excluded and should be reported under the category of 'Translational and applied research'.

3.3.4 Protection of the natural environment in the interests of the health or welfare of human beings or animals

This purpose includes studies aimed at investigating and understanding phenomena such as environmental pollution, loss of biodiversity, and epidemiology studies in wild animals.

This category excludes any regulatory use of animals for ecotoxicology purposes.

3.3.5 Preservation of species

This includes actions in relation to a life-threatening or debilitating condition in which human beings are endangered, and no other species or alternative method would suffice in order to achieve the aims of the procedure.

3.3.6 Higher education or training for the acquisition, maintenance or improvement of vocational skills

This includes training to acquire and maintain practical competence in techniques as required under Article 23(2) of the Directive and Regulation 43 of the S.I.

3.3.7 Maintenance of colonies of established genetically altered animals, not used in other procedures

This category describes animals required for the maintenance of colonies of genetically altered animals of established lines with an intended harmful phenotype and which have exhibited pain, suffering, distress or lasting harm as a consequence of the harmful genotype. The intended purpose for which the line is being bred is not recorded.

This excludes all animals needed for the creation of a new genetically altered line and those used in other procedures (other than creation/breeding).

3.3.8 Forensic enquiries

This includes the use of animals by forensic pathologists for legal investigations.

3.4 Section D – ~~Non-technical p~~Project summary

This section provides more detailed project information.

3.4.1 Project objectives

The project objectives including the scientific unknowns or scientific or clinical needs being addressed should be outlined briefly.

3.4.2 Project benefits

The potential benefits likely to derive from this project should be detailed and should include the expected benefits of the project to society or value to knowledge advancement. In the case of projects that are to be undertaken to satisfy regulatory requirements described by Article 42 of Directive 2010/63/EU, the appropriate reference to the requirements should be stated.

~~3.4.3 Species and number of animals~~

~~The species and approximate number of animals expected to be used in the study must be provided~~

~~3.4.4~~3.4.3 Summary of procedures, ~~E~~expected adverse effects and expected severity of procedures

A brief summary of the procedures used throughout the project should be included in this section. The expected adverse effects of the procedures on the animal must be described in detail, including the expected level of severity of each procedure. ~~and the fate of the animals once the procedure has been completed.~~ The overall severity of the project should also be ~~included.~~

3.4.4 Fate of the animals

The fate of the animals at the end of the project should be detailed in this section (e.g. humanely euthanised for tissue collection, returned to the herd, etc.).

3.5 Section E – Application of the 3Rs - ~~(~~r**R**eplacement, r**R**eduction and r**R**efinement~~)~~

3.5.1 Replacement

Outline why animals are required for this project, the non-animal alternatives that were considered for this project and the reasons why any available non-animal alternatives could not be used.

3.5.2 Reduction

Explain how the minimum number of animals is assured for this project including any statistical methods employed to determine the minimum number of animals.

3.5.3 Refinement

Explain the choice of species, why the animal model(s) used are the most refined in relation to the scientific objectives of the project. Explain the general measures to be taken to minimise harm to the animals.

4 ADMINISTRATIVE DETAILS

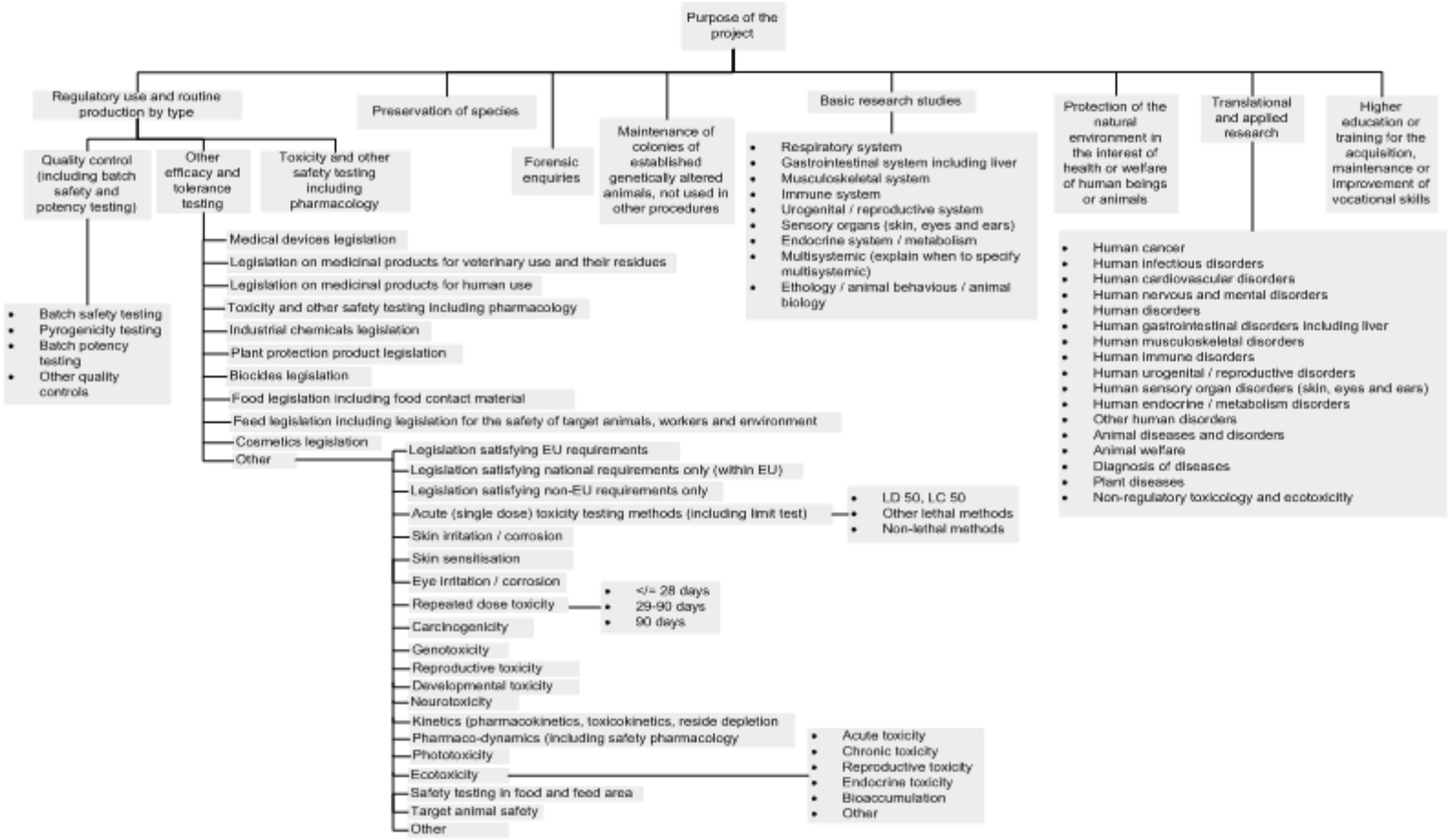
An NTPS must be submitted as part of a project application. The HPRA expects that following the authorisation of the relevant project, the NTPS will be uploaded at periodic intervals to the HPRA website. The timing of the uploading of the NTPS will depend on the number of projects approved and on logistical considerations, but is expected to follow within a maximum of six months of the authorisation of the project.

Queries in respect of the NTPS application requirements can be made by telephone, fax, and e-mail or by post to the following address:

Scientific Animal Protection Section
Veterinary Sciences Department,
Health Products Regulatory Authority,
Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2.
DO2 XP77

Tel: +353 1 676 4971
Fax: +353 1 676 7836
E-mail: sap@hpra.ie

APPENDIX I PROJECT CATEGORIES FOR SELECTION OF PROJECT PURPOSE



APPENDIX II EXAMPLE OF A NON-TECHNICAL PROJECT SUMMARY

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Non-technical Project Summary for a Project under Scientific Animal Protection Legislation
~~Non-technical Project Summary for a Project under Directive 2010/63/EU and S.I. No. 543 of 2012~~

This form is to be completed in **simplified lay language**, by the project manager or designated deputy project manager. For details of the requirements, please see the 'Guide to completing a non-technical project summary under scientific animal protection legislation'. Please ensure that for electronic submissions this document is submitted in **Word document format**.

Please note that **Section A is confidential** and will not be made publicly accessible. Sections B, C, D and E will be made publicly accessible on the HPRA website.
~~*This form is to be completed in simplified lay language, by the project manager or designated deputy project manager. For details of the requirements, please see the Guide to completing a non-technical project summary under Directive 2010/63/EU and S.I. No. 543 of 2012.*~~

~~*Please note that Section A is confidential and will not be made publically accessible. Sections B, C, D and E will be made publically accessible. Do not include any confidential information or information relating to the intellectual property of the project work in these sections.*~~

SECTION A: APPLICANT DETAILS

Name of project manager:	Mr Joe Bloggs
Individual authorisation number:	AExxxxx/Ixxx
Name of primary user establishment:	University of Ireland

SECTION B: PROJECT INFORMATION

Project title, to include the word 'research' or 'regulatory' (≤300 characters):

Research: Understanding bone marrow failure in leukaemia using a mouse model
State the species and number of animals expected to be used in this project:
500 mice
State expected duration of the project work (months):
60 months
Insert project keywords below (≤10 words – ~~please ensure to include species to be used~~the species used must be included):
Tumour; leukaemia; chemotherapy; radiation; mice

SECTION C: PROJECT PURPOSE

Enter the purpose(s) of the project (including appropriate subfields) from Appendix I of the *Guide to completing a non-technical project summary under scientific animal protection legislation* (this should match the purpose and sub-fields selected in the application form):
Translational and applied research - human cancer

SECTION D: PROJECT SUMMARY

This section must be written in a clear and concise manner using plain language understandable to a non-expert i.e. succinct and avoiding the use of highly technical terms. Where technical terms are unavoidable, they should be explained in layperson's terms. Do not include any confidential information or information relating to the intellectual property of the project work in this section.

Summarise, in lay terms, the project background and main project objectives, including the scientific unknowns or scientific or clinical needs being addressed. Please ensure that the context/background of the project is clear to a layperson (≤1500 characters):
Leukaemia is a cancer of the bone marrow. Treatment of adults with leukaemia is unsatisfactory with only a minority being cured. Drugs to treat acute myeloid leukaemia, were discovered in the 1960s, but no more effective drugs have been discovered since then. For a common type of adult leukaemia, acute myeloid leukaemia, most patients die from the disease despite chemotherapy. New approaches to developing drugs are required. A problem with leukaemia is that it appears to go away completely, but relapses after treatment has ended. This may be because a few 'tough' leukaemia cells (leukaemic stem cells) survive and grow again. This study will investigate how leukaemia cells dominate the bone marrow and make it stop producing normal blood cells such as red blood cells (that carry oxygen round the body) or white blood cells (that fight infection). Mice with deficient immune systems will be used, following transplantation with human leukaemic cells, to assess the effects of new drugs. Although assessment in cells in test-tubes will provide some information, the effects need to be followed over a longer time period in an animal to ensure all the leukaemic cells have been killed and relapses do not occur.
Detail the potential benefits likely to derive from this project and why this is necessary socially or scientifically (≤1500 characters):
The overall aim of the work is to improve understanding of leukaemia and to develop improved treatments for patients, especially to prevent relapses. This is important because leukaemia can be fatal, and current chemotherapy treatments are limited by high relapse rates and intense toxic side effects on patients due to the high doses required. Alternative therapeutic strategies are urgently required to improve patient outcomes.
Summarise each of the procedures the animals will undergo, the expected adverse effects and the expected severity of these procedures on the animals:
The animal's own bone marrow will be depleted by injecting a drug, or by radiation. This will cause tiredness and reduced appetite for about a week. This procedure is classified as moderate in severity. Leukaemia will then be induced by intravenous injection of leukaemic bone marrow. This procedure is classified as moderate in severity. Mice with leukaemia may become lethargic and lose weight.

What is the fate of the animals at the end of the project (e.g. humanely euthanised for tissue collection, returned to herd, etc.)? (≤300 characters):?
Animals will be humanely euthanised at the end of the study.

SECTION E: APPLICATION OF THE 3RS – REPLACEMENT, REDUCTION AND REFINEMENT

REPLACEMENT **Provide details as to why animals need to be used for this project and why non-animal alternatives could not be used (≤1500 characters):**
Human leukaemia cells grow poorly and only for short periods (a few days) once taken out of a living body and maintained in cell culture systems. This prevents the study of anything but short-term effects in the test tube. Given that leukaemias take weeks to months to develop, other methods must be used to study leukaemia cells. Immunodeficient mice exist that do not reject human bone marrow cells. Human bone marrow cells can be transplanted into these mice. Similarly, leukaemia cells can be transplanted into the mice. This allows for the study of how the leukaemias grow over several weeks. Therefore, live animals are required to achieve the objectives of this study.
REDUCTION **Provide details on how the use of minimum numbers of animals can be assured (≤1500 characters):**
The estimated number of animals is based on the research team's experience of designing these types of studies. A statistician was consulted when designing the study to ensure that the minimum number of animals are going to be used, while still being able to obtain scientifically robust results.
REFINEMENT **Explain the choice of species and why the animal model(s) to be used are the most refined. (≤750 characters):** ~~Summarise the general measures to be taken to minimise harm to the animals, e.g. provision of anaesthesia, pain relief, environmental enrichment, etc. (≤ 1500 characters):~~ ~~Finally, if any animal welfare issues arise, a veterinarian will be consulted.~~

Mice are the most refined animal model as the results obtained in these species are translatable to the human scenario. The strain of mouse being used in this study is immune-deficient. These mice will not reject the human-bone marrow cells that are injected into them. This animal model is widely used, therefore results of this study will be comparable to other published studies. The use of human cells in this project will increase the translatability of research for human studies.

Summarise the general measures to be taken to minimise harm to the animals, e.g. provision of anaesthesia, pain relief, environmental enrichment, etc. (≤ 1500 characters):

The immune-deficient mice will be kept in a protected environment to reduce the risk of infection. They will be group-housed with appropriate litter and nesting material. Mice will be provided with environmental enrichment materials such as nest boxes and Perspex tubes.

Chemotherapy and radiation treatments will cause some adverse effects. Doses are calculated to minimise these, consistent with the scientific objectives. In order to minimise pain and harm to the animals, a welfare scoresheet will be used daily to assess the animals. This ensures that action will be taken so that adverse effects beyond a pre-determined level are not exceeded. If animals get infections or become seriously ill, they will be humanely euthanised. Finally, if any animal welfare issues arise, a veterinarian will be consulted.

~~**SECTION A: APPLICANT DETAILS**~~

~~**PROJECT MANAGER**~~

~~Title: Mr.~~
~~First name: Joe~~
~~Surname: Bloggs~~
~~Individual authorisation number: AExxxxx/Ixxx~~

~~If no current individual authorisation number exists, state the date of application for an individual authorisation: N/A~~

~~**DEPUTY PROJECT MANAGER** *(if applicable)*~~

~~Title: N/A~~
~~First name: N/A~~
~~Surname: N/A~~
~~Individual authorisation number: N/A~~

~~If no current individual authorisation number exists, please state the date of application for an individual authorisation: N/A~~

PRIMARY ESTABLISHMENT

Establishment authorisation number: AExxxxx
Address where the project will be conducted:
Address 1: University of Ireland
Address 2: College Road
Address 3: Dublin
County: Co. Dublin

SECTION B: PROJECT INFORMATION

Project title (≤ 500 characters):
Research: Understanding bone marrow failure in leukaemia using a mouse model.

State expected duration of the project work (months):
60 months

Insert project keywords below (≤ 5 words):
Tumour; leukaemia; chemotherapy; radiation; mice

SECTION C: PROJECT PURPOSE

Select the purpose of the project from Appendix I of the *Guide to completing a non-technical project summary under Scientific Animal Protection Legislation*:
Transitional and applied research, human cancer

SECTION D: NON-TECHNICAL PROJECT SUMMARY

Describe the project objectives, including the scientific unknowns or scientific or clinical needs being addressed (≤ 5000 characters):
Leukaemia is a cancer of the bone marrow. Treatment of adults with leukaemia is unsatisfactory with only a minority being cured. Drugs against acute myeloid leukaemia, were discovered in the 1960s, but no more effective drugs have been discovered since then. For a common type of adult leukaemia, acute myeloid leukaemia, most patients die from the disease despite chemotherapy. New approaches to developing drugs are required.
A problem with leukaemia is that it appears to go away completely, but relapses after treatment has ended.
This may be because a few 'tough' leukaemia cells (leukaemic stem cells) survive and grow again. We will study how leukaemia cells dominate the bone marrow and make it stop

producing normal blood cells such as red blood cells (that carry oxygen round the body) or white blood cells (that fight infection). Mice with deficient immune systems will be used, following transplantation with human leukaemic cells, to assess the effects of new drugs. Although assessment in cells in test tubes will provide some information, we need to follow the effects over a longer time period in an animal to ensure all the leukaemic cells have been killed and relapses do not occur.

Detail the potential benefits likely to derive from this project (≤ 5000 characters):
The overall aim of the work is to improve understanding of leukaemia and to develop improved treatments for patients, especially to prevent relapses.

State the species and approximate number of animals expected to be used in this project:
Up to 5000 mice over a period of 5 years.

Describe the expected adverse effects on the animals, the expected level of severity and the fate of the animals (≤ 5000 characters):
The animal's own bone marrow will be depleted by injecting a drug or by radiation. This will cause tiredness and reduced appetite for about a week. Leukaemia will then be induced by intravenous injection of leukaemic bone marrow. Mice with leukaemia may become lethargic and lose weight. The expected level of severity is moderate. Animals will be humanely killed at the end of the study.

SECTION E: APPLICATION OF THE 3RS – REPLACEMENT, REDUCTION AND REFINEMENT

REPLACEMENT

Provide details as to why animals need to be used for this project and why non-animal alternatives could not be used (≤ 5000 characters):
Human leukaemia cells grow poorly and only for short periods (a few days) once taken out of a living body and maintained in cell culture systems. This prevents us from studying anything but short term effects in the test tube. Given that leukaemias take weeks to months to develop, we need other ways to study leukaemia cells. Immunodeficient mice exist that do not reject human bone marrow cells. We can transplant human bone marrow cells into these mice. Similarly, we can transplant leukaemia cells into the mice. This allows us to study how the leukaemias grow over several weeks.

REDUCTION

Provide details on how the use of minimum numbers of animals can be assured (≤ 5000 characters):

~~The estimated number of animals is based on our current experience of designing these types of studies. We consult with a biostatistician before conducting each study to ensure that we are using the minimum number of animals to achieve the desired result.~~

~~**REFINEMENT**~~

~~Explain the choice of species, why the animal model(s) used are the most refined and explain the general measures to be taken to minimise harm to the animals (≤ 5000 characters):~~
~~The immune-deficient mice will be kept in a protected environment to reduce the risk of infection. They will be group-housed with appropriate litter, nesting material and nest boxes.~~
~~Chemotherapy and radiation treatments will cause some adverse effects. Doses are calculated to minimise these, consistent with the scientific objectives.~~
~~If animals get infections or become seriously ill, they will be humanely killed.~~