Early Phase clinical trials: Toolkit for expert scientific review

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The patient

Source: Australianclinicaltrials.gov

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Clinical Trials - A Patient's Journey

This story follows the journey of a patient, her specialist and the clinical trial researcher during a clinical trial

Leslie was diagnosed with lobular breast cancer in August 2009. Shortly after her oncologist Dr Ross Jennings advised her of a suitable clinical trial.

Participants

Leonie Young, Chair of the Australia and New Zealand Breast Cancer Trials Group's Consumer Advisory Panel

I know that I have benefited from the results of breast cancer clinical trials and that more women are surviving cancer today than ever before.

Bradley Selmon Mesothelioma trial participant, Chris O'Brien Lifehouse and Royal Prince Alfred Hospital

I feel this clinical trial has saved my life

John Suckling, Bowel Cancer clinical trial participant

I was… sympathetically and thoroughly monitored both during the treatment and for the years afterwards.

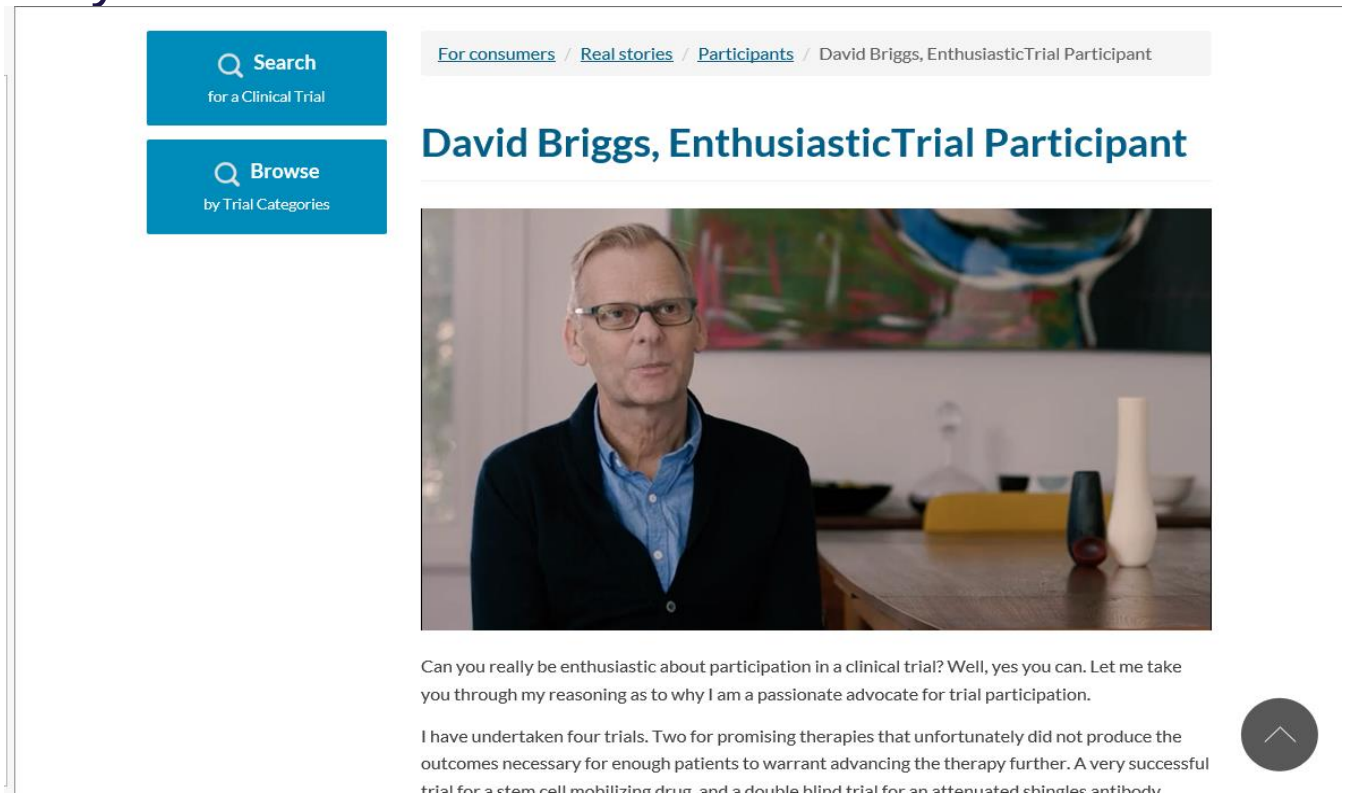
Heather Byrnes, Multiple Sclerosis (MS) clinical trial participant, Wesley

If it helped me, it will help many others in the future, in the world's journey to find a reason and a cure for

A remarkable story

Source: Australianclinicaltrials.gov

This patient has multiple myeloma (1996) and has participated in 4 clinical trials. He has had several stem cell transplantations, one aided by a trial.



Introduction – Early phase clinical trials

Reason for the Toolkit

- To equip ethics committees, researchers, sponsors and expert scientific reviewers to perform high quality review for early phase clinical trials
- To address a gap in guidance

There is an identified need for guidance and tools for scientific expert review for the ethics review process.

Clinical trials: the regulatory environment (TGA)

"The clinical trial environment in Australia is broad and there are various responsibilities resting with trial sponsors, HRECs, the approving authority (institution), investigators and Commonwealth and state and territory governments."

What is the regulatory environment for clinical trials?

"Efficient ethics and regulatory framework

Australia has a fast and pragmatic regulatory pathway for clinical trials. Under the Clinical Trials Notification (CTN) scheme administered by the Therapeutic Goods Administration (TGA), research proposals are submitted directly to Australian human research ethics committees (HRECs) which assume the primary review responsibility for ethical and scientific review. The usual review cycle takes only 4 to 8 weeks and is based on the submission of a protocol, investigator brochure and if required, an independent toxicology report. This effective and efficient process avoids costly preparation of extensive regulatory applications and means that research can start much sooner.

The TGA also administers the Clinical Trials Exemption (CTX) scheme, under which proposals are submitted to the TGA for scientific review followed by ethical review conducted by the HREC."

Source: https://www.australianclinicaltrials.gov.au/

Victorian Managed Insurance Authority (VMIA)

Historically, the VMIA produced a *"Protocol for Review of First in Human Research Proposals under the CTN Scheme (2006)"* containing SOPs and two expert review proformas.

Currently there is a VMIA *"Risk and Insurance Guide (2015)"* that is centred around insurance and indemnity matters only.

What has changed in the clinical trials environment? New therapies

Advances in knowledge, influence of genetic and molecular approaches to therapies

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), Cas9 genome editing technology

Used to target selected stretches of genetic code to cut DNA at a specific site (e.g. mutation) to add or delete pieces of genetic material, or to make changes to the patient DNA by replacing an existing segment with a customized DNA sequence.

CAR-T (Chimeric Antigen Receptor)

An individuals' own T cells are collected and a gene (or partial sequence) for a selected receptor is added (forming a chimera) that binds to a certain protein on the patient's cancer cells, then large numbers of CAR-T cells are grown and given to the patient by infusion. The CAR-T cells are able to bind to an antigen on the cancer cells and kill them.

New therapies

Immunological approaches include:

PD-1/PDL1 (checkpoint inhibitors)

Normally immune T-cells attach to cancer cells and PD1 (programmed cell death) proteins are expressed on the T-cells to kill those cancer cells.

Cancer cells express a **PD-1 ligand** that binds to PD-1 and inactivates the T-cells ability to kill cancer cells.

New immunotherapies called anti-PD-1 and anti-PD-L1 aim not to kill cancer cells directly but to **block the pathway that shields tumour cells** from the immune system killing mechanism. Thereby enabling cancer cell death.

New therapies

Oncolytic immunotherapies harness the power of specific viruses to preferentially infect and kill cancer cells.

For example CAVATAK®, is a proprietary formulation of the common cold Coxsackievirus Type A21 (CVA21) developed by Viralytics, who presented here last year.

CAVATAK acts by seeking out and attaching itself to a protein that is highly expressed on the surface of many cancer cells (ICAM-1). Once attached to this protein, the virus is then able to insert itself into the cancer cell, replicate, and burst the cancer cell apart (lysis) it then spreads and replicates this cycle of destruction. During the CAVATAK process, tumour cell fragments are released, which can potentially activate the body's own immune system by identifying the cancerous tumour cells as foreign.

Toolkit for expert scientific review

Advances in knowledge and the influence of genetic, molecular and immunological approaches to therapies has introduced new complexity in scientific review for ethics

Types of therapeutic goods include:

- Medicines
- Devices, including In Vitro Diagnostic (IVD) devices
- Biologicals

Early phase trials

“Early phase trials are no longer defined as traditional Phase I trials. Early phase trials can be broadly defined as non-therapeutic, exploratory trials in human participants who may be healthy volunteers or have a specific disease.”

Source: TGA Clinical Trial Handbook (2018)

Medicines

TGA definition

*"Therapeutic goods (other than biologicals) that are represented to achieve, or are likely to achieve, their principal **intended action by pharmacological, chemical, immunological or metabolic means** in or on the body of a human; and any other therapeutic goods declared by the Secretary…."*

Classification of Medicines

Class	Risk	Examples
FTIH	high	Study to determine safety, tolerability and pharmacokinetics of a medicine in healthy volunteers
FTIP	high	Study to determine safety, tolerability and pharmacokinetics of a medicine in patients
Phase I	high	Study to evaluate the safety and tolerability of a drug at increasing doses in patients

Medical Devices

“TGA definition *A medical device is:*

- *any **instrument, apparatus, appliance, material or other article** (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:*
- *diagnosis, prevention, monitoring, treatment or alleviation of disease;*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;*
- *investigation, replacement or modification of the anatomy or of a physiological process;*
- *control of conception;*
- *and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means; or*
- *an accessory to such an instrument, apparatus, appliance, material or other article.”*

Classification of medical devices

The classification of clinical trial stages of a medical device uses a set of rules based on:

- the manufacturer’s intended use of the device; level of risk to patients, users and other persons (the probability of occurrence of harm and the severity of that harm); degree of invasiveness in the human body; and duration of use

There are two separate classifications for medical devices. For example, these may refer to Class of medical devices and In Vitro Diagnostic (IVD) devices

Classification of medical devices (cont)

Medical device

Class	Risk	Examples
Class IIb	medium - high	blood bags, dressings providing a temporary skin substitute, artificial eyes
Class III	high risk	biological heart valves, heparin coated catheters, meniscul joint fluid replacement
Active Implantable Medical Devices (AIMD)	high risk	implantable pacemakers, defibrillators

In Vitro Diagnostic (IVD) devices

Class	Risk	Examples
Class 3 IVD	moderate public risk or high personal risk	all tests intended for human genetic testing
Class 4 IVD	high public health risk	IVDs intended for detecting red blood cell antigens, antibodies

Biologicals

A Biological is a product made from, or that contains, human cells or human tissues, or live animal cells, tissues or organs and that is used to:

- treat or prevent disease, ailment, defect or injury
- diagnose a condition of a person
- alter the physiological processes of a person
- test the susceptibility of a person to disease
- replace or modify a person’s body parts

Biologicals

Biologicals are classified by the TGA into four risk-based classes:

- Class 3 and Class 4 biologicals are prepared using more complex methods
- Class 3 has the potential to alter the cells or tissue but not the biological properties and
- Class 4 are when biological properties have changed

Some products may be specified as Class 4 for another reason

Biologicals classification

Class	Level of Manipulation	Risk	Examples
Class 3	Prepared using more complex methods, methods do not change the biological properties of the product	medium	demineralised bone, cultured fibroblasts for skin repair, chondrocytes for cartilage repair
Class 4	Prepared using more complex methods, methods do change the biological properties of the product	high	**genetically modified cells**, dermal fibroblasts for skeletal muscle repair in primary myopathy, **chimeric antigen receptor genetically modified white bloods cells**

Choosing between the CTN and CTX schemes

"The main difference between the CTN and CTX schemes is our (TGA) level of involvement in reviewing data about the therapeutic goods before the clinical trial commences.

The choice of which scheme to use (CTN or CTX) lies firstly with the trial sponsor and then with the HREC that approves the protocol (except for certain Class 4 biologicals, which must be approved under the CTX scheme).

One of the determining factors for a HREC is whether the committee has access to appropriate scientific and technical expertise in order to assess the safety of the product. The approving authority takes the ultimate responsibility for determining whether the trial is allowed to proceed at the site."

Source: TGA Clinical Trial Handbook (2018)

Choosing between the CTN and CTX schemes

“If a HREC feels that it requires additional expertise to review a CTN, it may seek advice from external authorities or it may seek to collaborate with another HREC that has the required expertise.

A HREC may determine that it does not have access to the appropriate scientific and technical expertise to review the proposed trial under the CTN scheme and recommend review under the CTX scheme.”

Source: TGA Clinical Trial Handbook (2018)

CTN and CTX schemes

"Medicines and biologicals The CTN scheme may be used for earlier phase studies if there is adequate preclinical information available, especially regarding safety.

The CTX route is generally for high risk or novel treatments, such as gene therapy, where there is no or limited knowledge of safety. Under the biologicals framework, the CTX scheme is mandatory for a clinical trial of any Class 4 biological unless:

· evidence from previous clinical use supports the use of the biological. For example, the safety of the product has been evaluated in an earlier phase clinical trial. The effect on safety of changes in the manufacture of the product, or of use of the product for a new clinical indication, must be carefully considered; or

· a national regulatory body with comparable regulatory requirements has approved a clinical trial for an equivalent indication. Seek advice from us (TGA) if you intend to use this provision. You will need to provide evidence that the safety review by the overseas regulator is equivalent to that which would be performed by us. In addition, the product used in the trial approved by the overseas regulator must be the same as that in the proposed trial. The effect on safety of changes in the manufacture of the product, or of use of the product for a new clinical indication, must be carefully considered."

Source: TGA Clinical Trial Handbook (2018)

Toolkit:
Scientific Expert Review proformas

Proforma	Content
Medicines	• Clinical trial information • Investigational product information • Primary pharmacodynamics • Dose response relationship • Supplement information (as relevant)
Medical Devices	• Clinical trial information • Investigational product information • Primary data/Preclinical testing • Quality management & regulatory compliance • Summary • Supplement information (as relevant)
Biologicals	• Clinical trial information • Investigational product information • Primary data • Dose and response relationship • Supplement information (as relevant)
Toxicology	• Clinical trial information • Primary pharmacodynamics • Dose and response relationship • Pharmacokinetics • Additional toxicology

Toolkit:
Scientific Expert Review - supplements

Supplement	Content
Immunology	• Clinical trial information • Additional immunology information • Risk evaluation
Biologicals, Biodynamics and Kinetics	• Clinical trial information • Dynamics and kinetics • Risk evaluation

Toolkit Guidance

- **Scientific Expert Reviewers**
- **Investigators and Sponsors**
- **Ethics committee**
- **Research office**

The guidance is detailed and specific for each of the above roles

Toolkit Governance documents

- **Conflict of Interest Declaration Form**
- **Deed of Acknowledgement of Obligations as an Expert Reviewer**
- **Insurance and Indemnity**

Release of the Toolkit

Due to be released in Q3 2018

Communications:

- Clinical Trials and Research website (Coordinating Office, DHHS)
- Streamline E-bulletin
- Contact the Coordinating Office: Email: multisite.ethics@dhhs.vic.gov.au

Acknowledgements

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