The Australian and New Zealand College of Anaesthetists ANZCA Clinical Trials Network

Large Trials in Anaesthesia and Perioperative Medicine

Ms Sophie Wallace and Ms Jaspreet Sidhu

AGENDA

- ANZCA Clinical Trials Network
- Investigator initiated clinical trials in Anaesthesia
- Funding sources – NHMRC, College Foundation, hospital grants / awards
- Trial management – Project Office perspective
  - ETHICS and governance
  - CTRA negotiation
  - CTNs
- NMA – past, present, future?

ANZCA CLINICAL TRIALS NETWORK

DISCLAIMER

The views and opinions expressed in this presentation are based on our individual and collective experiences only and we encourage our colleagues and peers in this room to share your experience at the end of this session as there may be discipline specific issues that we have not addressed today.

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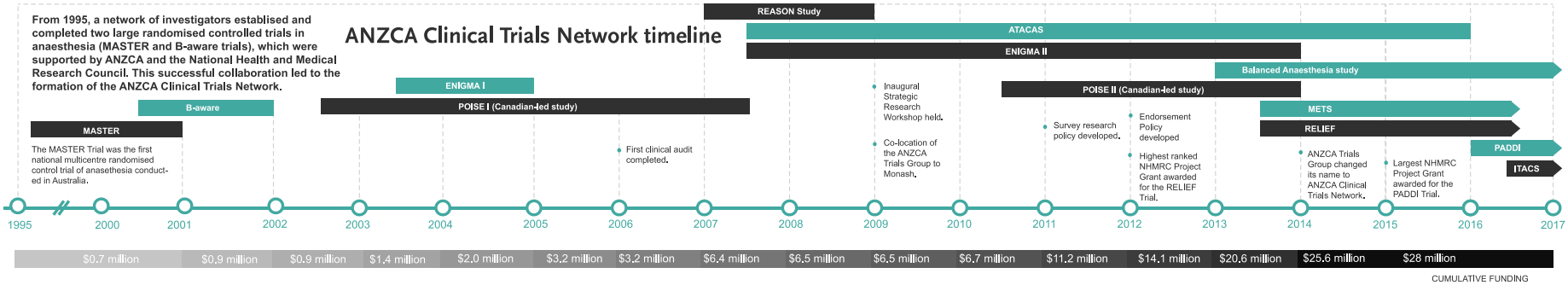
CELEBRATING OVER 20 YEARS IN ANAESTHESIA RESEARCH



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AT A GLANCE

$33 million in total research funding

15 multicentre trials across **130** sites in **12** countries

33,234 patients randomised into ANZCA trials

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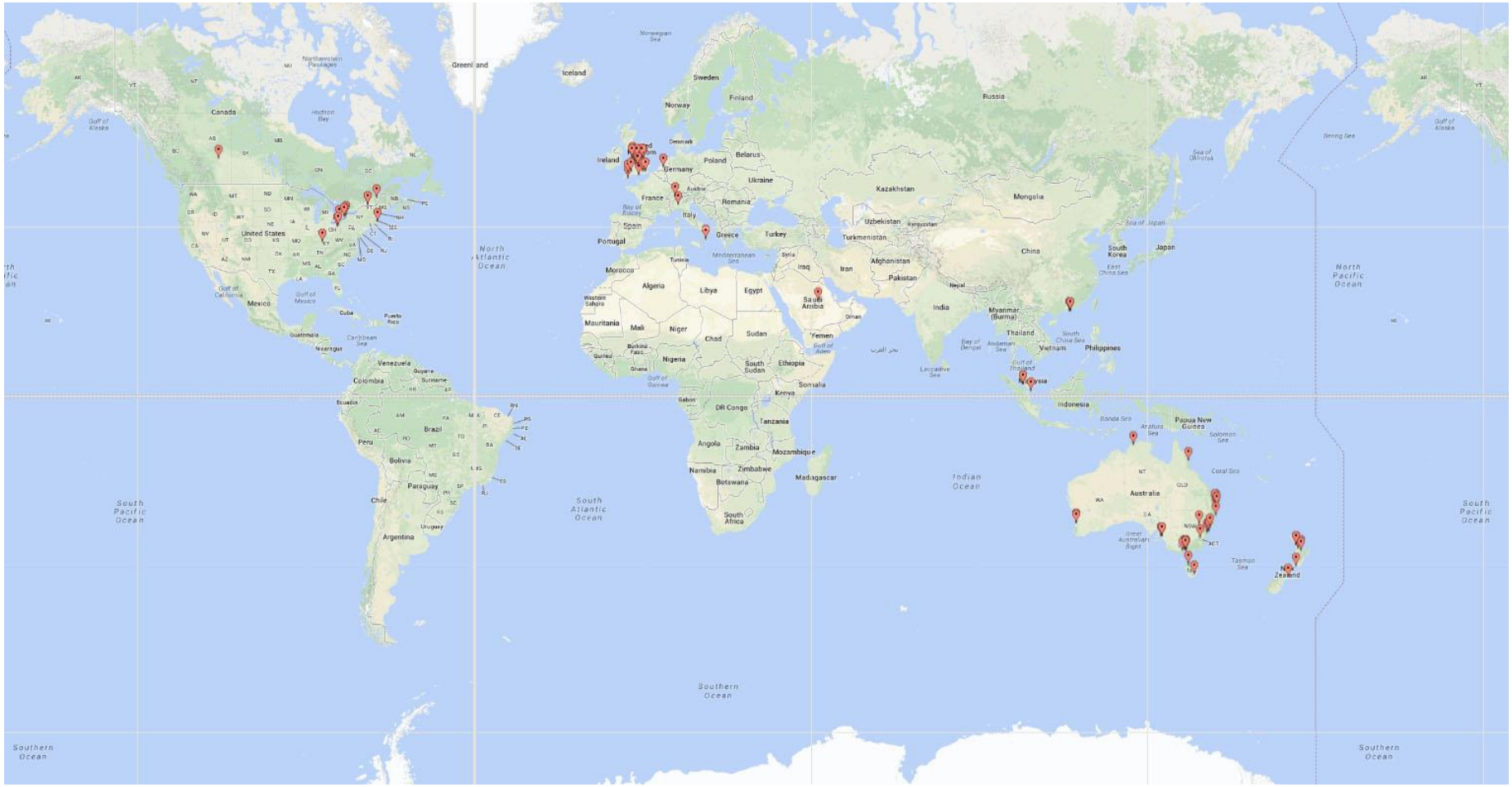
SITES



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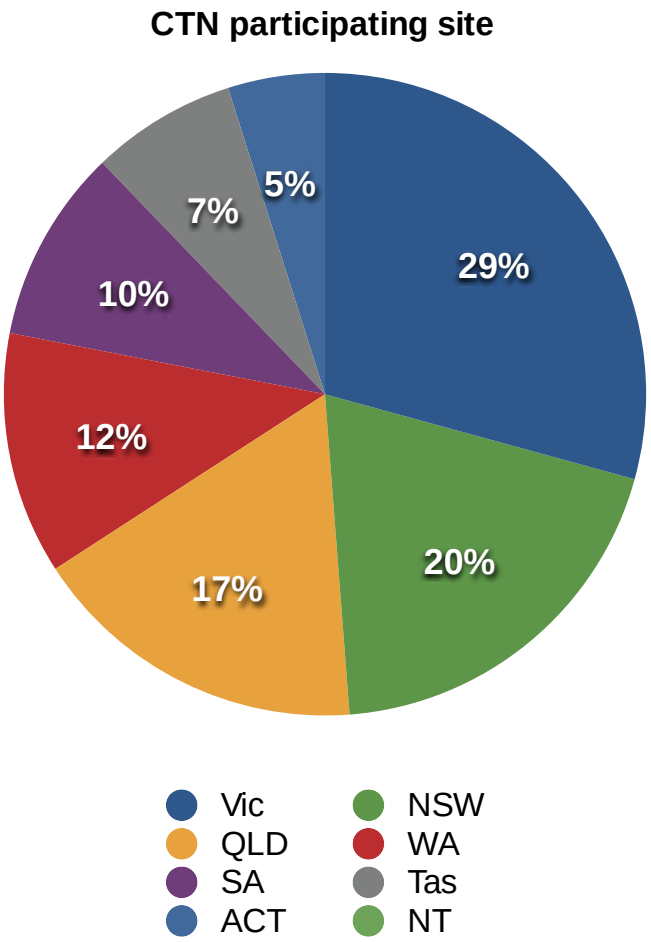
Australian sites



Vic – 12

NSW – 8

QLD – 7

WA – 5

SA – 4

Tas – 3

ACT – 2

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ANZCA CTN Trials

	Completed Trial
ANZCA Research Grant	MASTER
ANZCA Research Grant	B-Aware
	POISE
ANZCA Research Grant	ENIGMA
ANZCA Research Grant	REASON
ANZCA Research Grant	ENIGMA II
	POISE-2
	Neurovision
	ISOS
	Current Trials
ANZCA Research Grant	ATACAS
ANZCA Pilot Grant	BALANCED
ANZCA Pilot Grant	RELIEF
ANZCA Research Grant	METS
	PADDI
ANZCA Pilot Grant	ROCKET

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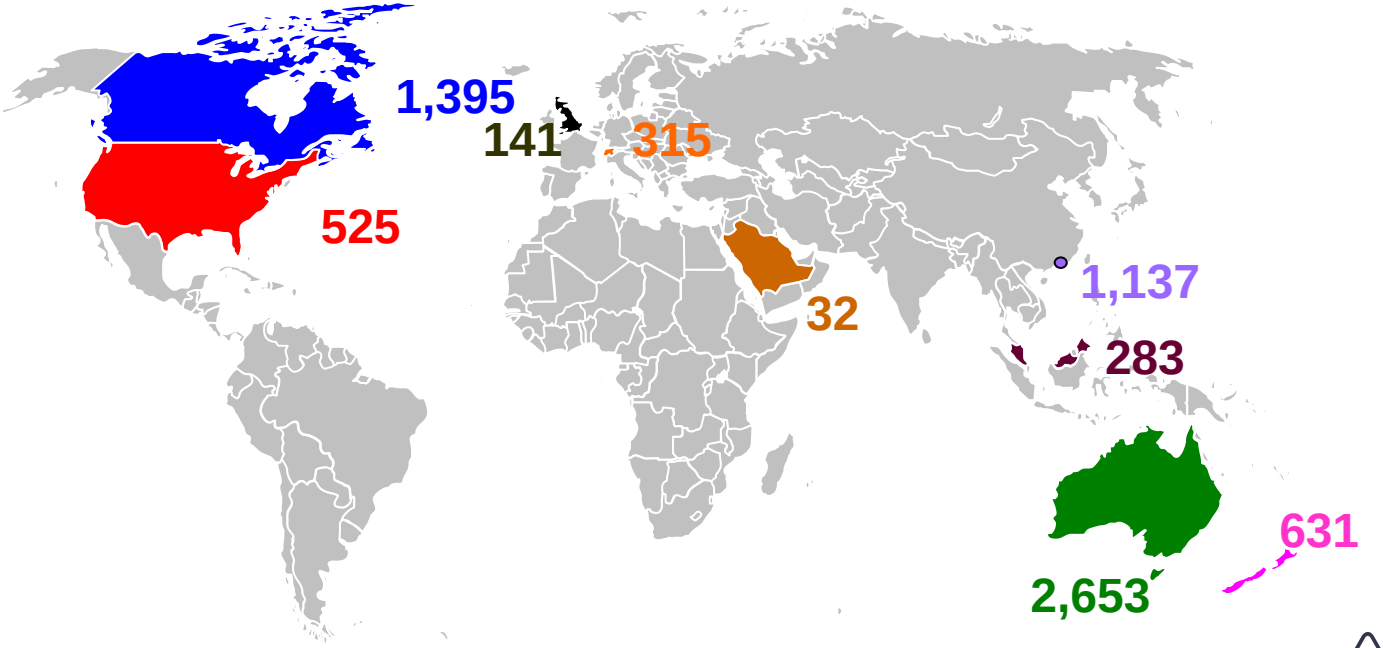
ENIGMA II

- Large, multicentre 5 year trial
- 7106 patients in 45 hospitals worldwide
- Long term effects of nitrous oxide in patients with coronary artery disease undergoing major surgery
- Primary outcome – composite of death and cardiovascular complications



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PADDI Trial

Perioperative ADministration of Dexamethasone and Infection

- N = 8880
- Dexamethasone 8mg or placebo
- Inclusion criteria
  - Adult patients, skin incision >5cm, surgery over 2hr, minimum hospital stay of 1 night
- Primary outcome
  - Surgical site infection within 30 days of surgery

Largest value NHMRC project grant in 2014

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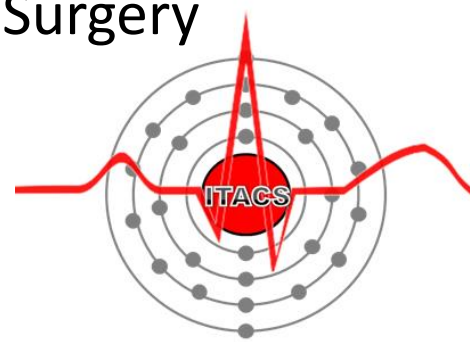
ITACS Trial

IV iron for Treatment of Anaemia before Cardiac Surgery



- N = 1000
- Inclusion criteria
  - Adult patients with anaemia undergoing elective surgery
- Primary outcome
  - Days alive out of hospital to 30 days of surgery

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Ethics & Governance processes...

Trial	Total sites (countries)	No. sites in Aus	Ethics approach
MASTER	25 (6)	18	site based
B-Aware	21 (5)	17	site based
POISE*	190 (23)	15	site based
ENIGMA	24 (5)	14	site based
REASON	23 (2)	22	site based
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Balanced*	76 (8)	28	SERP
RELIEF	70 (6)	38	SERP
PADDI	70**(5)	56**	NMA
ITACS	32**(5)	12**	NMA

* international project office
** EOIs received

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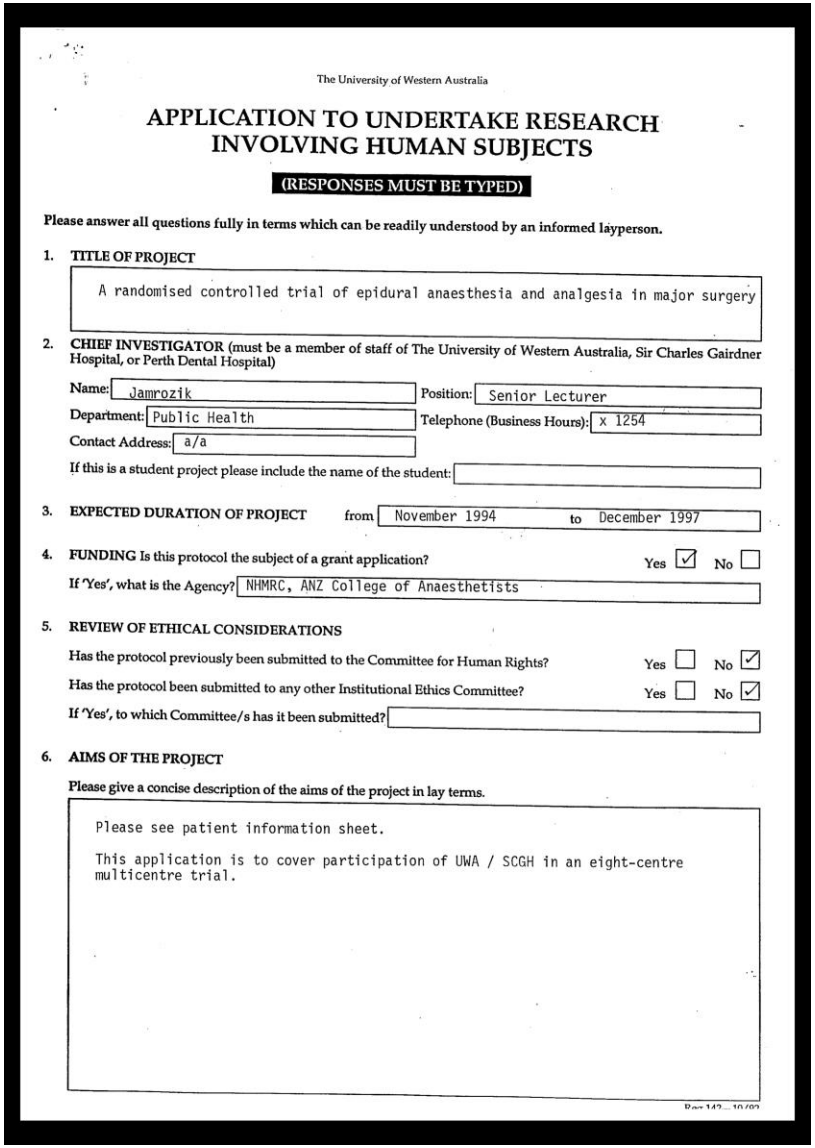
Ethics applications in the 90s



The University of Western Australia

APPLICATION TO UNDERTAKE RESEARCH INVOLVING HUMAN SUBJECTS

(RESPONSES MUST BE TYPED)

Please answer all questions fully in terms which can be readily understood by an informed layperson.

1. **TITLE OF PROJECT**

   A randomised controlled trial of epidural anaesthesia and analgesia in major surgery

2. **CHIEF INVESTIGATOR** (must be a member of staff of The University of Western Australia, Sir Charles Gairdner Hospital, or Perth Dental Hospital)

   Name: Jamrozik Position: Senior Lecturer

   Department: Public Health Telephone (Business Hours): x 1254

   Contact Address: a/a

   If this is a student project please include the name of the student:

3. **EXPECTED DURATION OF PROJECT** from November 1994 to December 1997

4. **FUNDING** Is this protocol the subject of a grant application? Yes ☑ No ☐

   If 'Yes', what is the Agency? NHMRC, ANZ College of Anaesthetists

5. **REVIEW OF ETHICAL CONSIDERATIONS**

   Has the protocol previously been submitted to the Committee for Human Rights? Yes ☐ No ☑

   Has the protocol been submitted to any other Institutional Ethics Committee? Yes ☐ No ☑

   If 'Yes', to which Committee/s has it been submitted?

6. **AIMS OF THE PROJECT**

   Please give a concise description of the aims of the project in lay terms.

   Please see patient information sheet.

   This application is to cover participation of UWA / SCGH in an eight-centre multicentre trial.

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Australian Trail of
Epidural Anaesthesia and Analgesia in Major Surgery

Information for Patients

Description

Two types of anaesthetic may be used for patients having the kind of operation planned for you. If the patient is given a conventional anaesthetic, he of she is given medications by injection into a vein. One of the drugs causes temporary unconsciousness, a second drug blocks pain, and a third drug paralyses all of the muscles in the body in order that the surgeon can have easy access to the field of surgery. This also requires the anaesthetist to control your breathing throughout the operation. After the operation, further doses of drugs to block pain are given by injection into a vein or muscle. Frequently, an **epidural** anaesthetic is used together with **conventional** general anaesthesia to reduce the stress of the surgery and to provide relief from pain after the operation. In these cases, an epidural drug is given through a fine plastic tube inserted in the middle of the patient's back just before the general anaesthetic is given.

Some anaesthetists and surgeons believe that reducing the stress of an operation by using an epidural anaesthetic decreases the complications of surgery and leads to a quicker recovery and earlier discharge form hospital. Many other anaesthetists and surgeons do not agree with this view.

The only way to resolve the uncertainty is to do an experiment in which some patients receive one type of anaesthetic and some patients the other type. For this reason, you are invited to take part in a trial which will compare conventional anaesthesia without an epidural with conventional anaesthesia with an epidural. Either type of anaesthetic is suitable for you, and you will receive all usual care before, during and after your surgery regardless of which anaesthetic you receive or whether you join the trial at all.

The risk of having an epidural with general anaesthesia versus the risk of not having an epidural with general anaesthesia is, in general, not known. As noted above, the reduction in stress associated with an epidural during surgery might reduce the rate of serious complications, such as heart attack, stroke and thrombosis. Patients with pre-existing medical problems who undergo major surgery may be at quite high risk - up to 50% of developing a significant complication during the first 14 days following the operation, regardless of the type of anaesthetic used. This reflects the risk of the surgery, not of the general or epidural anaesthesia. The rate of serious complications following either type of anaesthesia is very low, between 1 in 10,000 and 1 in 50,000. If an epidural does reduce the major complications of surgery, this would compensate for the small additional risk of the epidural itself. Side effects of general anaesthesia include nausea, vomiting, headaches and drowsiness. Side effects of epidurals include low blood pressure, nausea, vomiting, backache, headache and itching.

Eight major teaching hospitals in Victoria and Western Australia have agreed to take part in the trial. This agreement reflects the concern felt by many Australian specialists that the uncertainty as to whether epidural anaesthesia is better needs to be resolved. The eight hospital are the Royal Melbourne, Alfred, St. Vincent's, Austin and Heidelberg Repatriation Hospital in Melbourne and the Sir Charles Gardiner, Hollywood Private and King Edward Memorial Hospitals in Perth.

If you do agree to take part in the trial, the type of anaesthetic you receive will be decided by a random process. This helps to ensure that the patients in the two groups are equivalent for all other factors that might affect the outcome of the operation.

The doctors in charge of the experiment in this hospital are **Dr. Thomas Tan** , **Dr. Gerard Stainsby** and **Prof. Duncan Blake**. Please ask to speak to one of them or to **Fiona Libreri**, the Research Nurse working on the project, if you have any questions about the trial. Alternatively, you may wish to contact the Trial Office on telephone number (09) 389 1254.

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Multiple ethical review

- Printed copies
- Costs – Postage, paper, time
- Individual site queries

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Multiple ethical review

al HREC conducts its own ethical review of the research proposal (i.e. multiple ethical review occurring for one research proposal).

nvestigator has to handle requests from multiple HRECs.

s the outcome of multiple ethical reviews and may be required to enter into dialogue with all HRECs to achieve a consensus position.

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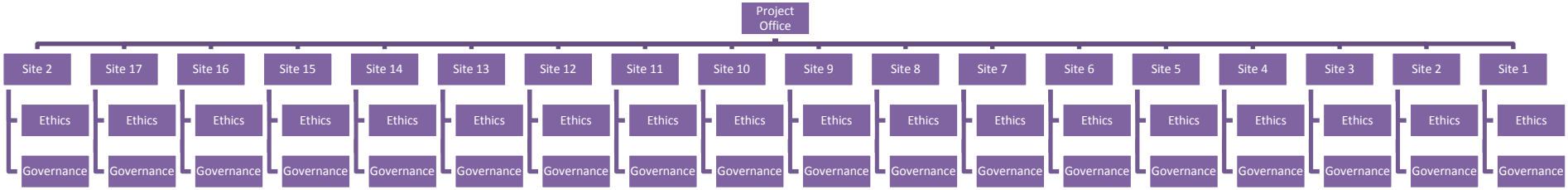
Multiple ethical review



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Multiple ethical review

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Single ethical review

esponse of one HREC.

ators at each participating institution provide the outcome of the single ethical review to their respective institution.

g institution uses the outcome of the single ethical review and their site-specific research governance information to determine esearch will commence at their institution.

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National Mutual Acceptance – The Principles

- **Efficiency** – agreed timeframes for processes and procedures are adopted in all jurisdictional systems
- **Trust** – the single ethics review of a multi-centre research proposal is accepted by institutions without re-review by their institutional HREC
- **Respect** – the National Approach accommodates the differences in jurisdictional statutory and administrative frameworks and institutional arrangements
- **Compliance** – single ethics review of multi- centre human research meets the requirements of the National Statement to protect human research participants as well as meeting relevant jurisdictional statutory and administrative frameworks

Source: www.nhmrc.gov.au/health-ethics/national-approach-single-ethical-review/what-meant-single-ethics-review

National Mutual Acceptance - Benefits

- Time from ethics review application to study start-up is shortened (savings in human and monetary resources)
- Australia's attractiveness as a place for international investment in commercially sponsored clinical trials is enhanced
- Public confidence in the rigour of Australia's system of ethics review is increased due to the standardisation of ethics review processes
- Roles and responsibilities are transparent

Q: Is there are gap between this theory and practise?

Source: www.nhmrc.gov.au/health-ethics

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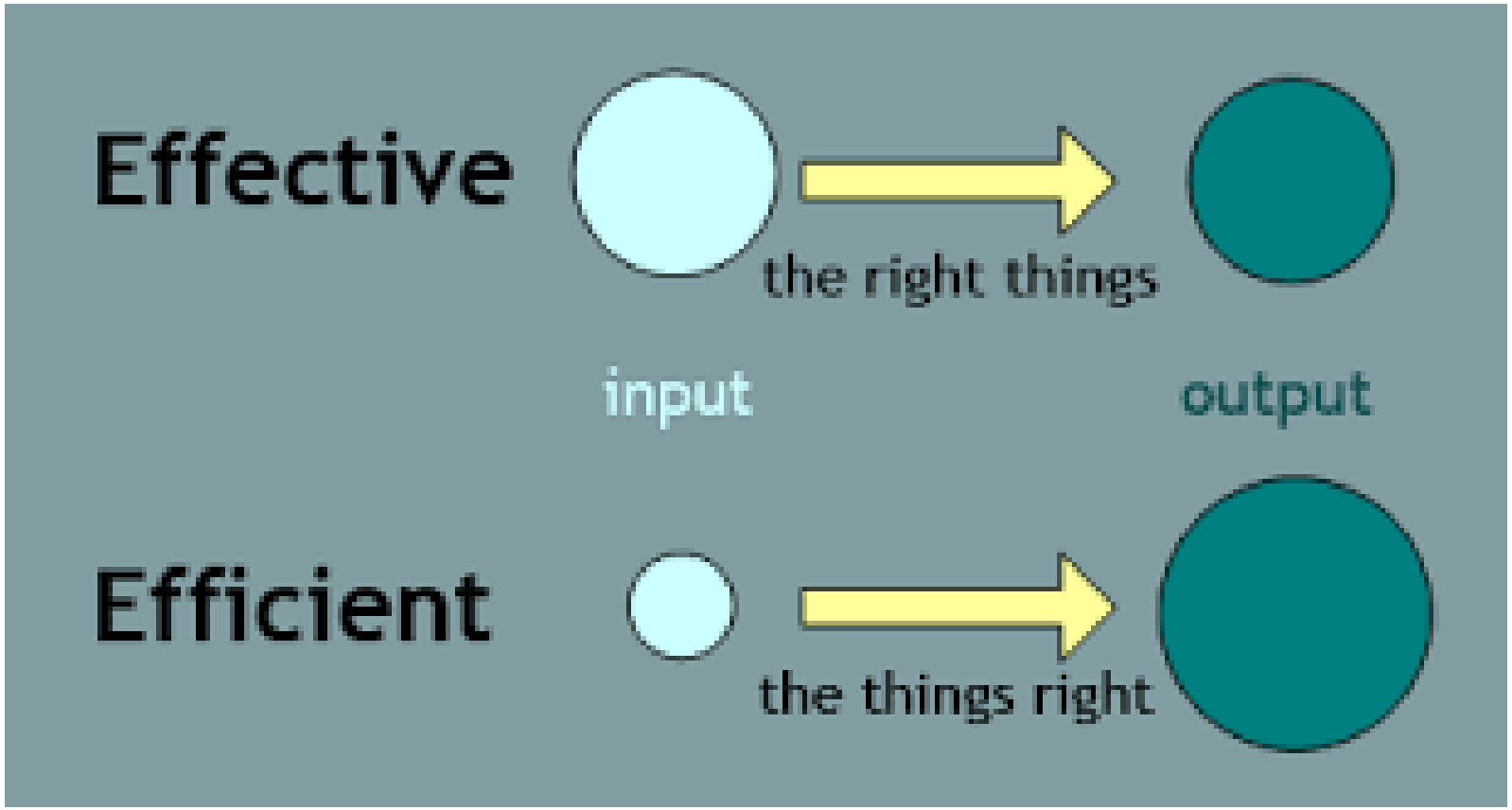
Can we see the benefits yet?



ANZCA CTN Trial - revisited

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Despite the changes…

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Challenges then…

- Duplication at individual sites
- Resource intensive
- Increased burden on ETHICS committees and CPI
  - Queries / clarifications
  - Multiple reviews
- Time to site start up
- Effort to coordinate between sites
- Lack of universal regulation
  - Site specific
  - Hard as manager to keep abreast of the various site specific regulations

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Current state

- All states and territories (however not completed rolled out)
- NEAF accepted by all
- Site specific documents (state regulations)
- E-signatures
- Inconsistencies between reporting SAEs due to trial / site specific requirements
- Private hospitals not part of NMA

Are there still challenges?

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The future…

- Agreement to use the Universal database platforms
  - ethicsforms
  - AuRED
- Increased support and training for use of these national systems
- Get rid of paper
- CTRAs
- CTN/CTX – TGA notifications

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Navigate | Documents | Transfer Form Temporarily | Authorisation | Submission | SSA | Project Progress | Email History

List | Upload

Any electronic documents already uploaded against the NEAF Application Form will automatically be uploaded against the SSA Form

Document Type	Document Upload Date	Document Date	Version	Size	Uploaded by Assessing Organisation	Tools
Covering Letter	(none)					
CTN Form	(none)					
CTX Form	(none)					
Drug data sheet	(none)					
GP/Consultant Information Sheets	(none)					
Interview Schedules / Topic Guides	(none)					
Investigator CV	(none)					
Investigator's Brochure	(none)					
Letter from Sponsor	(none)					
Letter Of Intention To Appeal	(none)					
Letter of invitation to participant	(none)					
Master Consent Form	(none)					
Master Participant Information Sheet	(none)					
Other	(none)					
Participant Information Sheet/Consent Form	(none)					
Peer Review	(none)					
Protocol	(none)					
Questionnaire	(none)					
Response to Request for Further Information	(none)					
Sample Diary/Patient Card	(none)					
Site Specific Consent Form	(none)					
Site Specific Participant Information Sheet	(none)					
Statistician Comments	(none)					
Summary/Synopsis	(none)					
Victorian-Specific Module	(none)					

Thank you

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