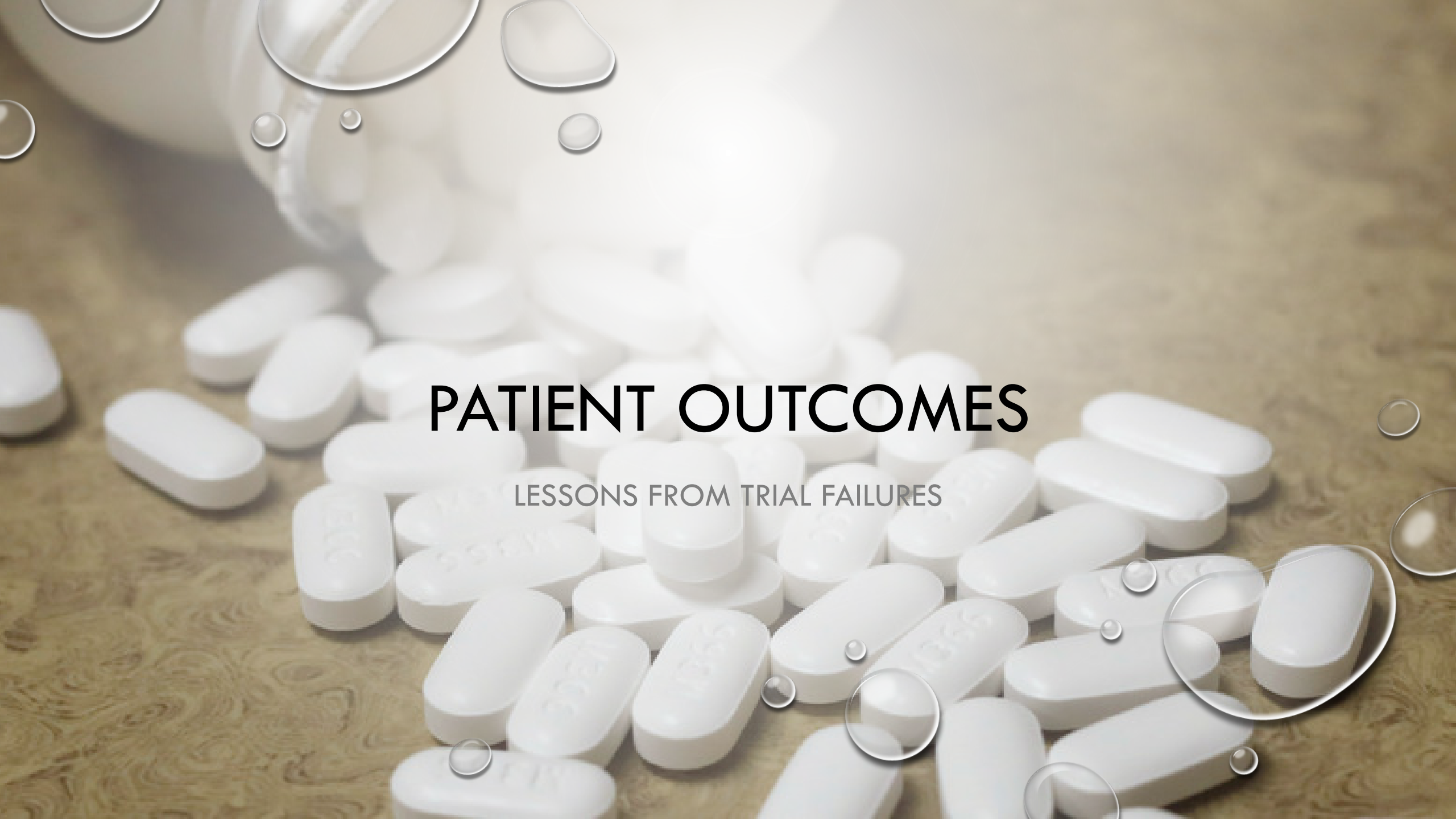


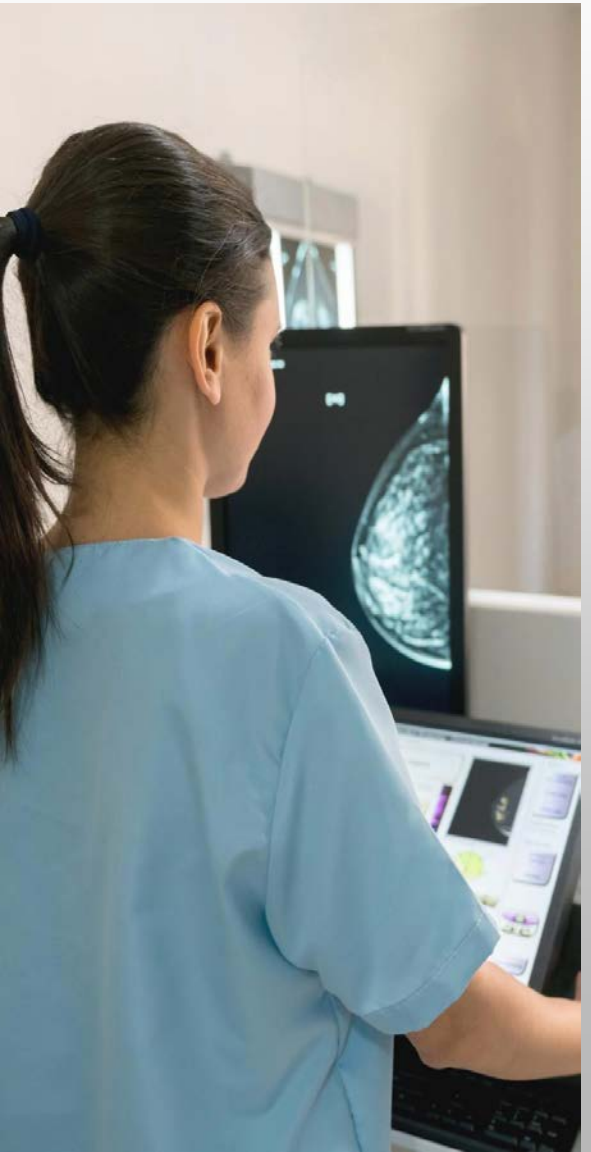
PATIENT OUTCOMES

LESSONS FROM TRIAL FAILURES

CLINICAL TRIAL PHASES

- PHASE 0 TRIALS – PILOT THESE COME BEFORE PHASE I TRIALS AND ARE USED TO TEST HOW THE BODY RESPONDS TO AN EXPERIMENTAL DRUG. IN THESE STUDIES, SMALL DOSES OF THE NEW DRUG ARE GIVEN ONCE OR FOR A SHORT TIME TO A VERY LIMITED NUMBER OF PEOPLE
- PHASE I– "*FIRST IN HUMAN*" ARE DONE TO TEST A NEW BIOMEDICAL INTERVENTION FOR THE FIRST TIME IN A SMALL GROUP OF PEOPLE (E.G. 20-80) TO EVALUATE SAFETY (E.G. TO DETERMINE A SAFE DOSAGE RANGE AND IDENTIFY SIDE EFFECTS). – *USUALLY HEALTHY PARTICIPANTS*
- PHASE II – "*EFFICACY*" INTERVENTION CONDUCTED IN A LARGER GROUP OF PEOPLE (TYPICALLY SEVERAL HUNDRED) TO DETERMINE EFFICACY (THAT IS, WHETHER IT WORKS AS INTENDED) AND TO FURTHER EVALUATE ITS SAFETY.
- PHASE III – "C*OMPARATIVE*" STUDIES ARE DONE TO STUDY THE EFFICACY OF AN INTERVENTION IN LARGE GROUPS OF TRIAL PARTICIPANTS (FROM SEVERAL HUNDRED TO SEVERAL THOUSAND) BY COMPARING THE INTERVENTION TO OTHER STANDARD OR EXPERIMENTAL INTERVENTIONS (OR TO NON-INTERVENTIONAL STANDARD CARE). PHASE III STUDIES ARE ALSO USED TO MONITOR ADVERSE EFFECTS AND TO COLLECT INFORMATION THAT WILL ALLOW THE INTERVENTION TO BE USED SAFELY.
- PHASE IV – "MARKET MONITORING" ARE DESIGNED TO MONITOR THE EFFECTIVENESS OF THE APPROVED INTERVENTION IN THE GENERAL POPULATION AND TO COLLECT INFORMATION ABOUT ANY ADVERSE EFFECTS ASSOCIATED WITH WIDESPREAD USE OVER LONGER PERIODS OF TIME. THEY MAY ALSO BE USED TO INVESTIGATE THE POTENTIAL USE OF THE INTERVENTION IN A DIFFERENT CONDITION, OR IN COMBINATION WITH OTHER THERAPIES.

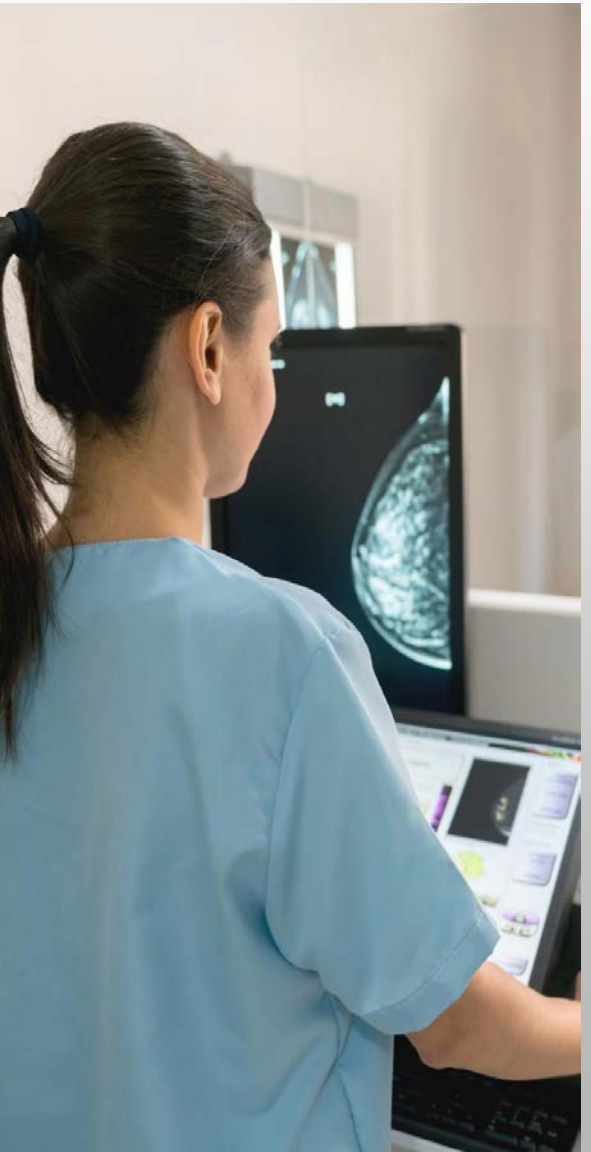
AUSTRALIAN WESTERN WHITE PINE TAXOL GROUP



Plant alkaloids are toxic and are a source of taxanes which have been used in chemo therapy to treat breast cancer.

- A clinical trial of a taxane derived from the Western Australian White Pine circa 1990 studied the effect of the taxane extract as a selective estrogen receptor modulator.
- At the time of study prognosis for treatment was poor with limited 5 year survival.
- Phase II study was proposed to test efficacy of the new compound.
  - Inclusion criteria stage 4 diagnosis.
  - restricted from alternate treatments.
  - A fully double blinded study.
    - Two arms – placebo, novel compound.

AUSTRALIAN WESTERN WHITE PINE TAXOL GROUP



Justice

Researchers recognised that stage 4 diagnosis meant that the placebo group were denied any alternate treatment. Whilst no effective alternate was claimed to be available it also precluded participants from other unproven techniques which may have been of benefit and interventions to extend life.

Resolution

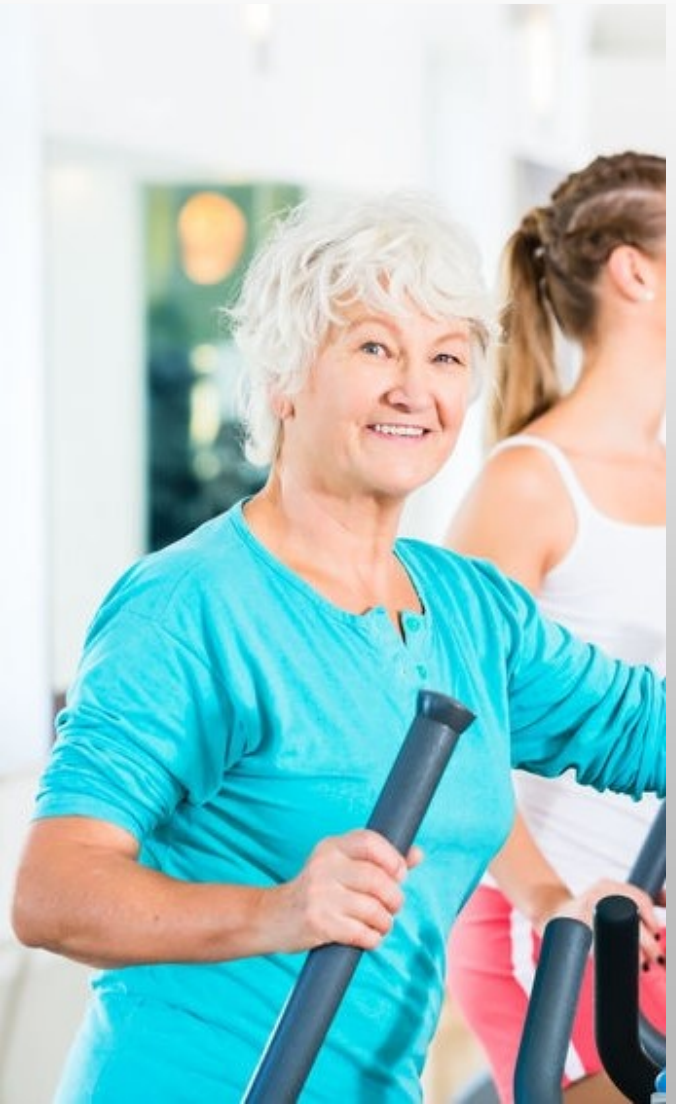
The research monitoring plan included a systematic staged partial deblending when a given proportion of the patients showed clinical signs of improvement. If the improvement was evident in the treatment group the study was to be halted and the treatment offered to all participants

Outcome

Due to treatment efficacy the study was halted prematurely and offered to all patients. 50% increase in survivability.

Dilemma – premature project closure damaged the scientific integrity of the study but resolved the justice issue. The question could be raised as to long term toxicity of the treatment.

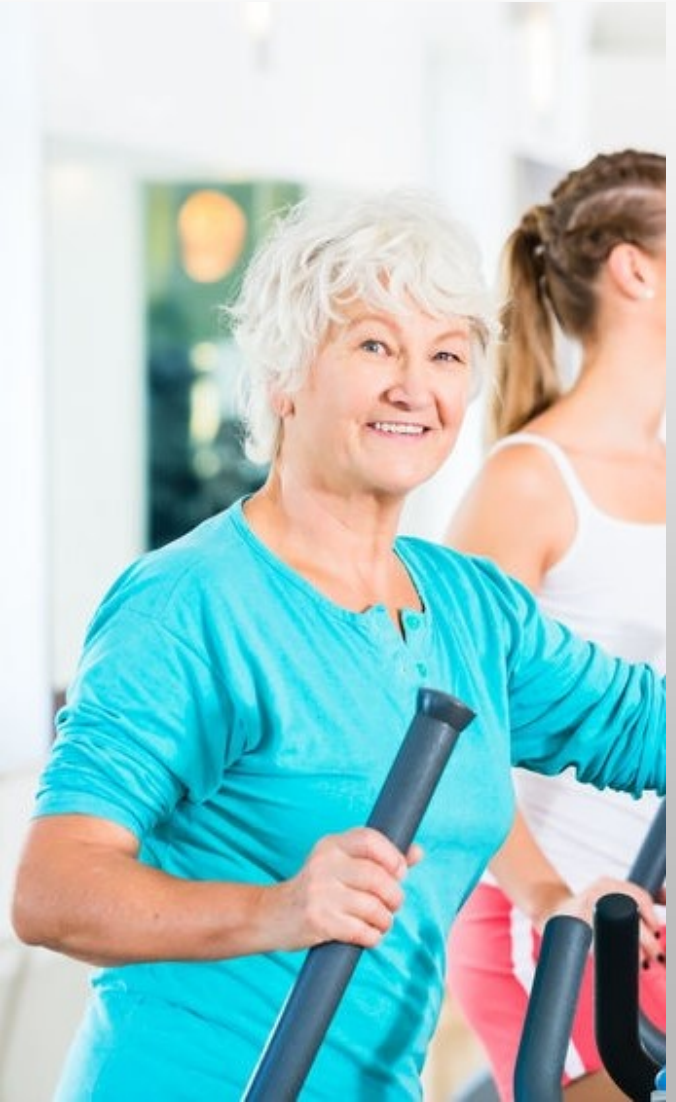
EXERCISE AND DIABETES



Type II Diabetes increases the risk of silent heart disease in women. Moderate exercise assists better dietary control of sugar levels and should lower cardiac risk in mature women with Type II diabetes.

- Phase 0 or is it Phase II trial of twice weekly moderate exercise in a sample of otherwise healthy women with Type II diabetes was conducted in South East Queensland..
- The study was proposed to test efficacy of the novel exercise regime .
  - Inclusion criteria Type II diabetes, female, age 60 + .
  - restricted from alternate treatments.
  - Twice weekly exercise in a gym at a university campus.
    - Dose arms – Low, Moderate exercise.
    - VO_2 Max, cardiac measures etc.

EXERCISE AND DIABETES



Benefit and Risk

Researchers presented a case that the benefit was very consistent with existing empirical data and exercise was protective. They assessed risk as 1:60,000 against an adverse event.

Resolution

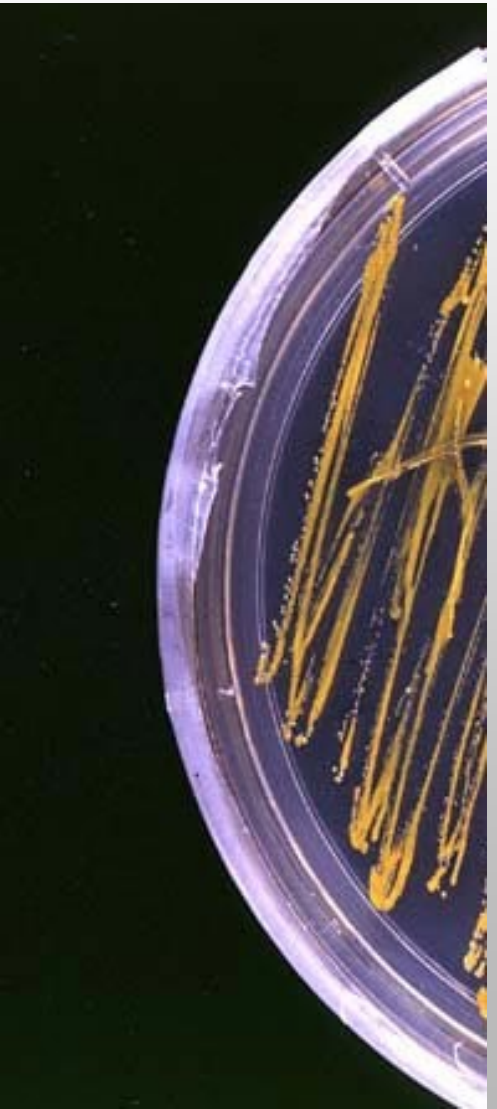
The reviewing committee identified the risk assessment as accurate or perhaps overstated and noted the diligence of the research team who had put in place;

- Crash cart
- Emergency physician
- Arrangement with local hospital ambulance services
- Entry arrangement at the university site.

Outcome

In a sample of 30 women 2 cardiac emergencies occurred in the one weekend. Provisions to mitigate risk were effective. After treatment one participant was healthy enough to continue the study. The other did not continue but received ongoing treatment for a previously undetected issue which was consequently well managed.

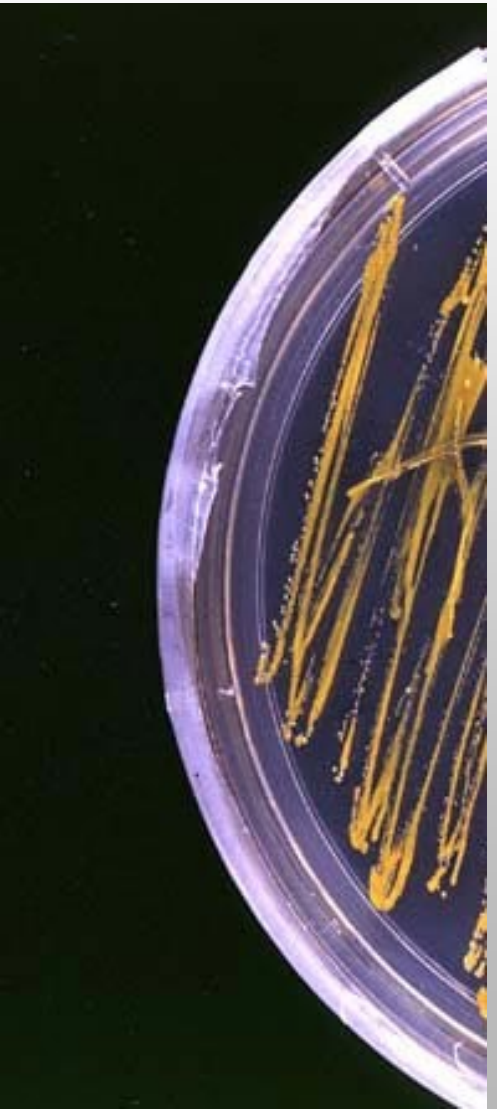
HIV TREATMENT
THERALIZUMAB



Early 2000's HIV treatment largely ineffective. Some work was being conducted in London at immune suppression activating T1 cells to attack HIV infected cells.

- Pre-clinical lab work indicated a promising monoclonal antibody with high specificity without evidence of toxicity to other tissues.
- Phase I First in human trial by PAREXEL in London in 2006
- At the time of study long term survivability was poor but management was improving.
- Phase I study was proposed to test safety.
  - Inclusion criteria HIV positive.
  - restricted from alternate treatments.
  - Small n study 6 HIV positive male volunteers.
  - Treatment does sub-clinical 0.1mg/kg (500 times < animal studies).
  - 2 hour protocol approved – actually administered within 20 minutes.

HIV TREATMENT
THERALIZUMAB



Benefit and Risk

In vitro, and animal studies showed aggressive disruption of virus infected cells but not other tissue. Dose very low, sample would benefit from a better than best practice treatment if effective.

Resolution

Study was approved. Men were all treated on the same day by intravenous delivery.

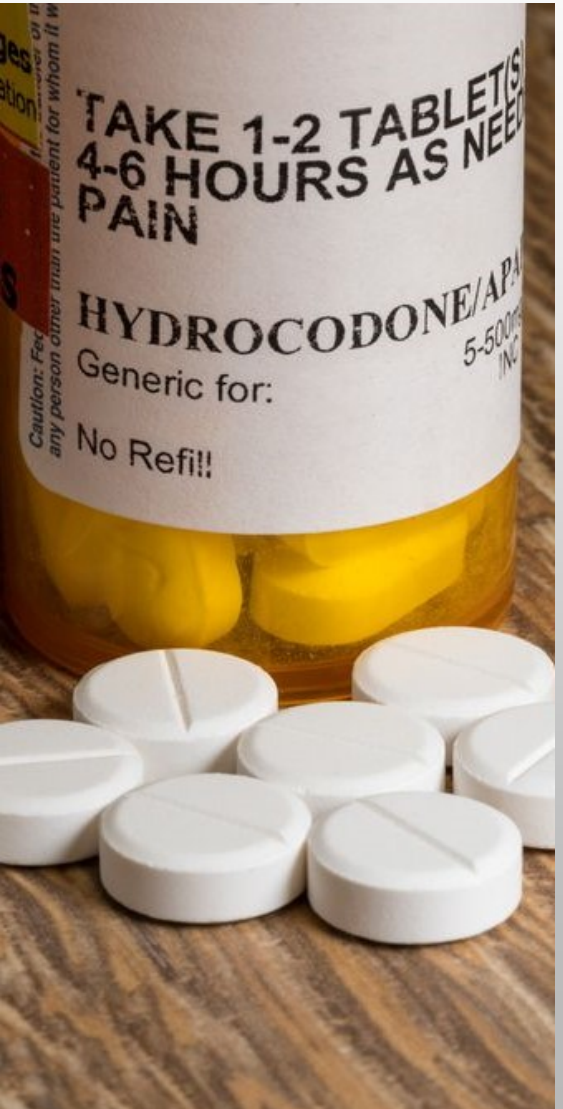
Outcome

Within 24 hours all 6 participants were seriously ill, 4 with multiple system failure. The 4 with multiple system failure had severely compromised health in long term follow-up.

As a result a recommendation was made that all subsequent ethics approvals for drug trials of first in human provide for adequate spacing of administration to participants at least 24 hrs to limit adverse reactions to the minimum number of participants.

Development of Theralizumab was discontinued.

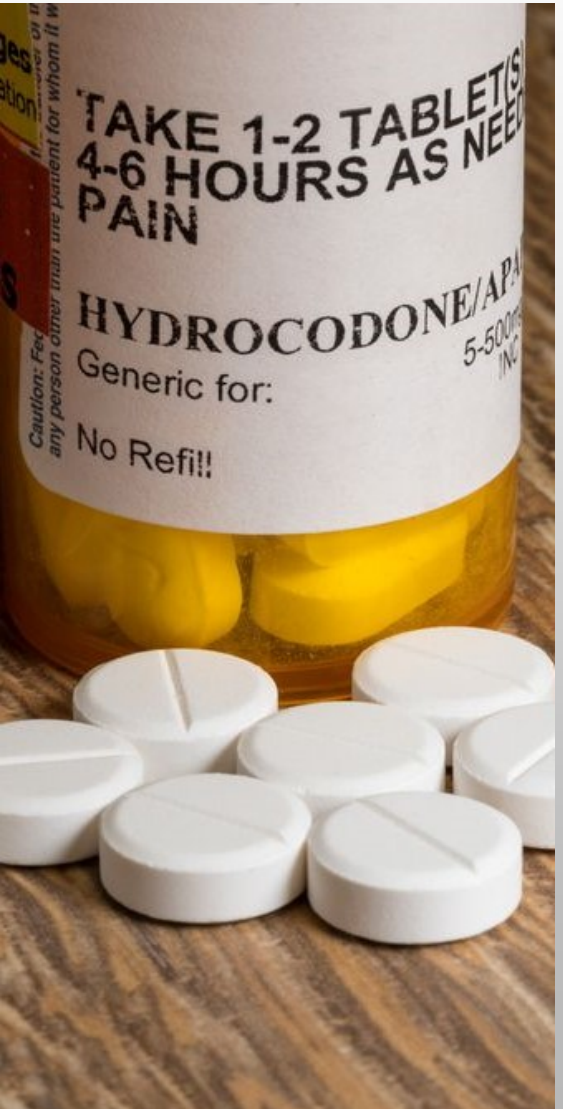
THE PAIN KILLER



January 2016 Portugese drug company Bial trialled a new pain killer BIA 10-2474. The compound interrupts the endocannaboid system.

- Phase I First in human trial by BIAL in Paris in 2016
- Described in the press at the time as a pain killer trial.
- Phase I study was proposed to test safety.
  - Healthy adults no known pathology.
  - Small n study 6 volunteers.

THE PAIN KILLER



Benefit and Risk
The new compound was described in early press reports as an analgesic and already in existing use for arthritis patients. Is this off-label use rather than a clinical trial?
The goal was to reduce neuropathic pain.

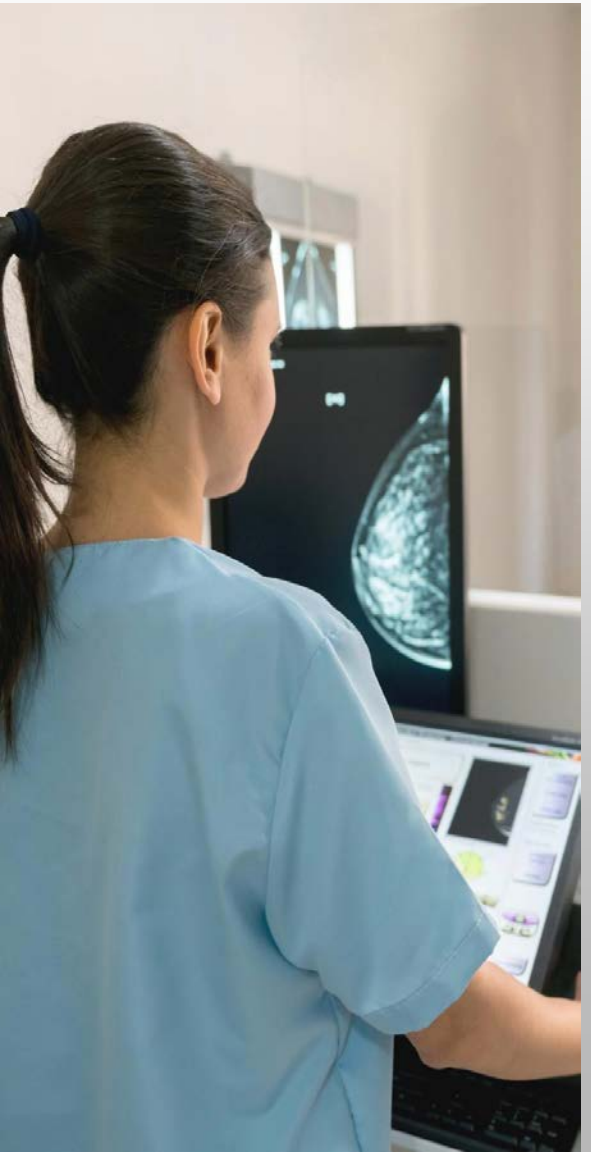
Resolution
Study was approved, on the basis of animal studies without supporting in vitro lab work. Details are difficult to come by due to French privacy laws.

Outcome
Using a staged incremental approach 84 participants had been exposed to 10 days at 20mg. Before a high dose 50mg trial was commenced on 8 patients with 2 placebo and 6 trial participants. after 5 days one trial patient was admitted to hospital with stroke like presentation. He subsequently died. The remaining 50mg participants all exhibited severe haemorrhagic lesions in the hypothalamus and pons. With lasting deficits.

European requirements for first in trial studies have been revised.

Development of BIA 10-2474 was discontinued.

TAXOLS REVISITED



Taxanes became widely adopted and survivability of breast cancer increased dramatically but Phase IV – monitoring – often not formally conducted by sponsors of original trials have raised questions as to the long term toxicity effects of Taxols. Especially in regard to liver function. Some debate as to if they should be withdrawn?

A range of pharmaceuticals are identified as efficacious in Phase II trials but show long term consequence in less structured long term data. There have been at least 176 significant drug withdrawals from long term monitoring reports. Often these are not formal followups by sponsors but reports to agencies like the TGA. Phase III, and Phase IV trials are less commonly reported than – Phase I and Phase II. This may present a false under representation of significance of risk.

But if survivability increased with taxanes and they are withdrawn from market to prevent longterm hepatic damage which is the greater ethical risk?

LESSONS

- THE CLEAR CLINICAL DESCRIPTIONS OF THE PHASES OF CLINICAL TRIALS ARE NOT AS DEFINITIVE AS THEY APPEAR.
- THE RISK OF CLINICAL TRIALS IS NOT STAGED BY LEVEL. ADVERSE EVENTS CAN OCCUR AT ANY LEVEL.
- CORRECT PREPARATION OF ADVERSE EVENTS MITIGATES THE RISK IN THE EVENT THAT THE WORST HAPPENS.
- THE BASIC PRINCIPLES OF ETHICS
    - SCIENTIFIC MERIT & INTEGRITY
    - JUSTICE
    - BENEFICENCE AND FREEDOM FROM HARM
    - RESPECT FOR PARTICIPANTS
- THE DESIRE FOR AN ADEQUATE SAMPLE DOES NOT ABSOLVE RESEARCHERS OF THE NECESSITY TO DISCLOSE THE NOVELTY, AND UNKNOWN RISK AND OF ANY REASONABLE ALTERNATIVE. TO DO OTHERWISE IS UNJUST, NOT RESPECTFUL AND HAS THE POTENTIAL FOR HARM.

SPIRIT STATEMENT & CHECKLIST

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