

Thoughts on the Evolution of the Trials Programme in Singapore

Tuberculosis Trials in Singapore

1940s to 1980s?

Tan Tock Seng Hospital collaboration
with UK MRC

2015 TRUNCATE-TB

1996

CTERU: The Beginning

CTERU

Aim to encourage and support
National and Regional Studies
particularly RCTs

Ongoing International Trials

Encourage collaboration with RCTs
initiated outside of Singapore

Planning

Collaboration begins well before
RCTs start and publications arise!

What was expected of CTERU?

Design
Conduct
Analysis
Reporting
Coordination

High Early Priority

Establishing (then Maintaining)
Regular contact with the
Investigators

Seeking wider collaboration

Two aims:

Establish Singapore as a Regional Hub
for RCTs

Increase recruitment to Singapore
initiated trials

All of the **Trials** initiated during my period as Director were published later

First RCT Publication

Colorectal Surgery, SGH

Tang C-L, ... , (2001) *British Journal of Surgery*

Open versus Laparoscopically Assisted colectomy
for colorectal cancer

[Component of UK MRC CLASSIC Trial]

Amazing Recruitment

250 patients in 2.5 years!

Earlier Publication

National Dental Centre

Poon, *et al* (1998) Commenting on a
Split-Mouth design to evaluate
photochemotherapy (PUVA) for oral
lichen planus

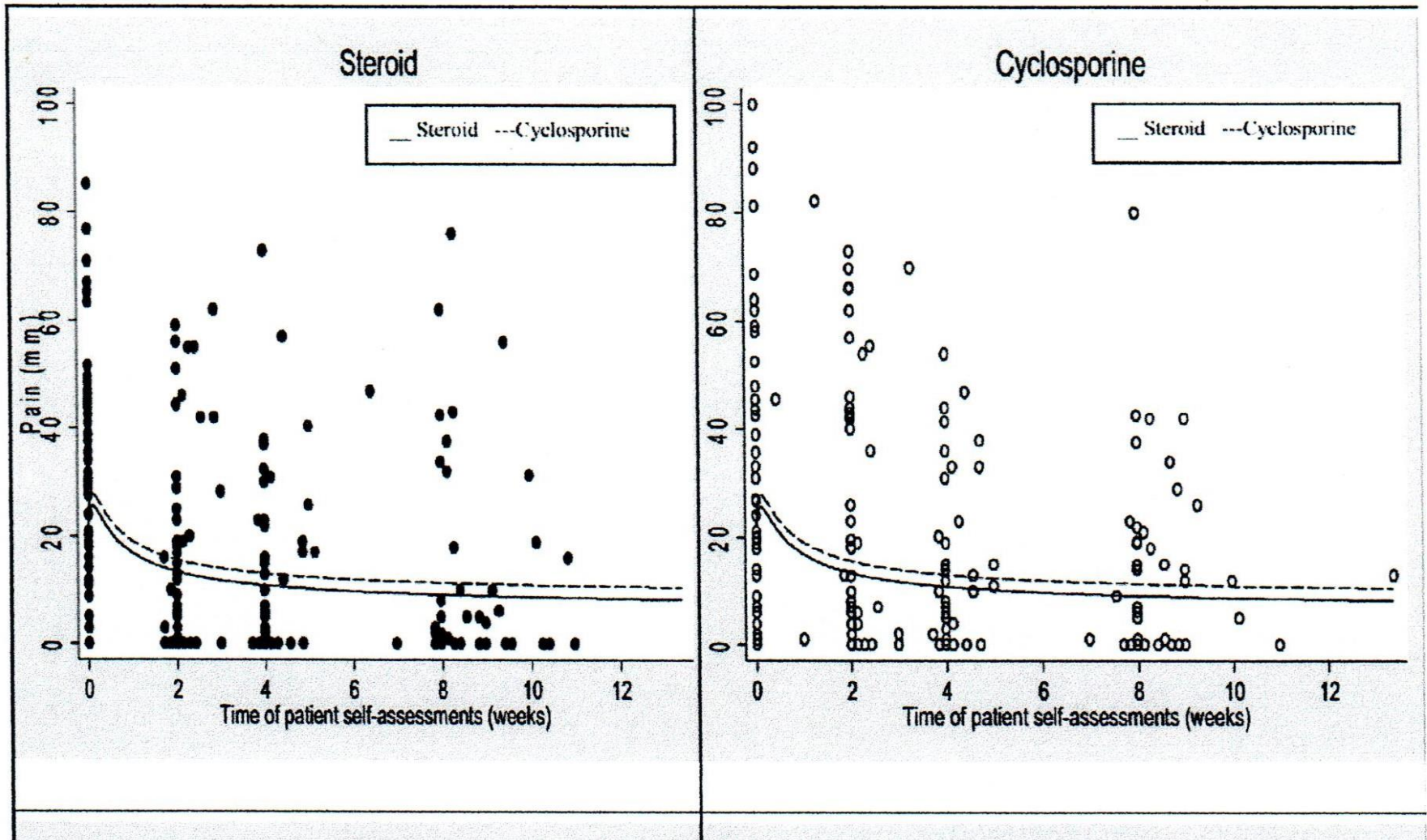
Arose while planning the Oral Lichen Planus trials with The National Dental Centre & The National Skin Centre

Oral Lichen Planus

Poon, *et al* (2006)

India, Singapore, South Korea

Pain Scores by Treatment Group



Role of Tamoxifen in Hepatocellular Carcinoma (HCC)

Pierce Chow, *et al*
(1998) *Lancet*

Arose while planning and
during the course of the
international AHCC01 trial

2002 Hepatocellular Carcinoma

Myanmar, Hong Kong, Singapore, Thailand, Indonesia, Malaysia,
South Korea, New Zealand, Australia

Chow PKH, *et al* (2002). High-dose tamoxifen
in the treatment of inoperable hepatocellular
carcinoma: A multicenter randomized trial.
Hepatology, **36**, 1221-1226

Role of Tamoxifen (TMX)

Placebo: TMX60: TMX120

2 : 1 : 2 Randomisation

International Trial: 329 entered

Role of Tamoxifen

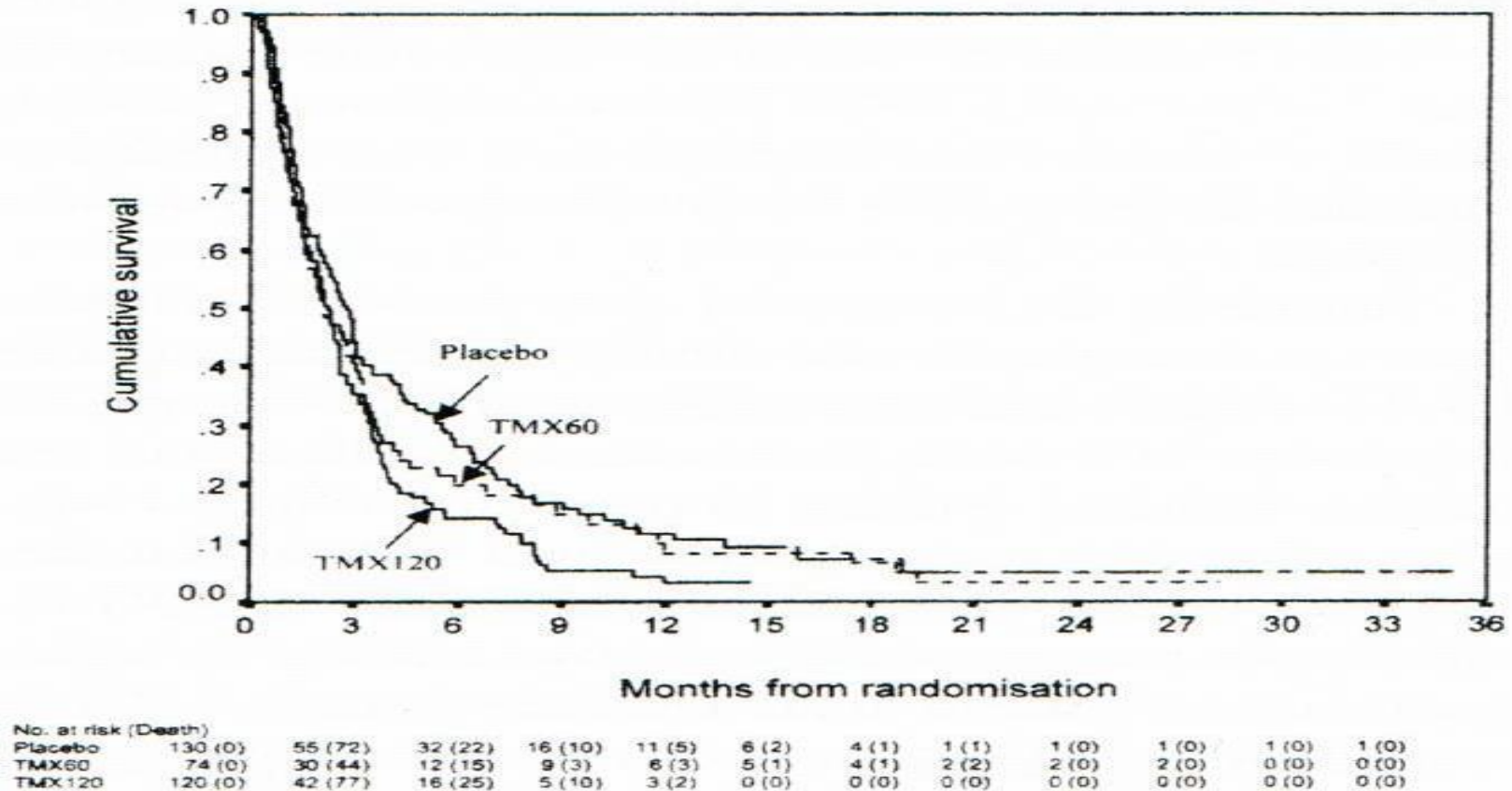


Fig. 2. Patient survival.

The ethics of randomized trials in the context of cleft palate research

SGH Burns Unit

Lee ST, *et al* (2000) *Plastic and Reconstructive Surgery*, 105, 1566-8

Arose during the course
of the MEBO
randomised trial

Moist Exposed Burn Ointment (MEBO)

v

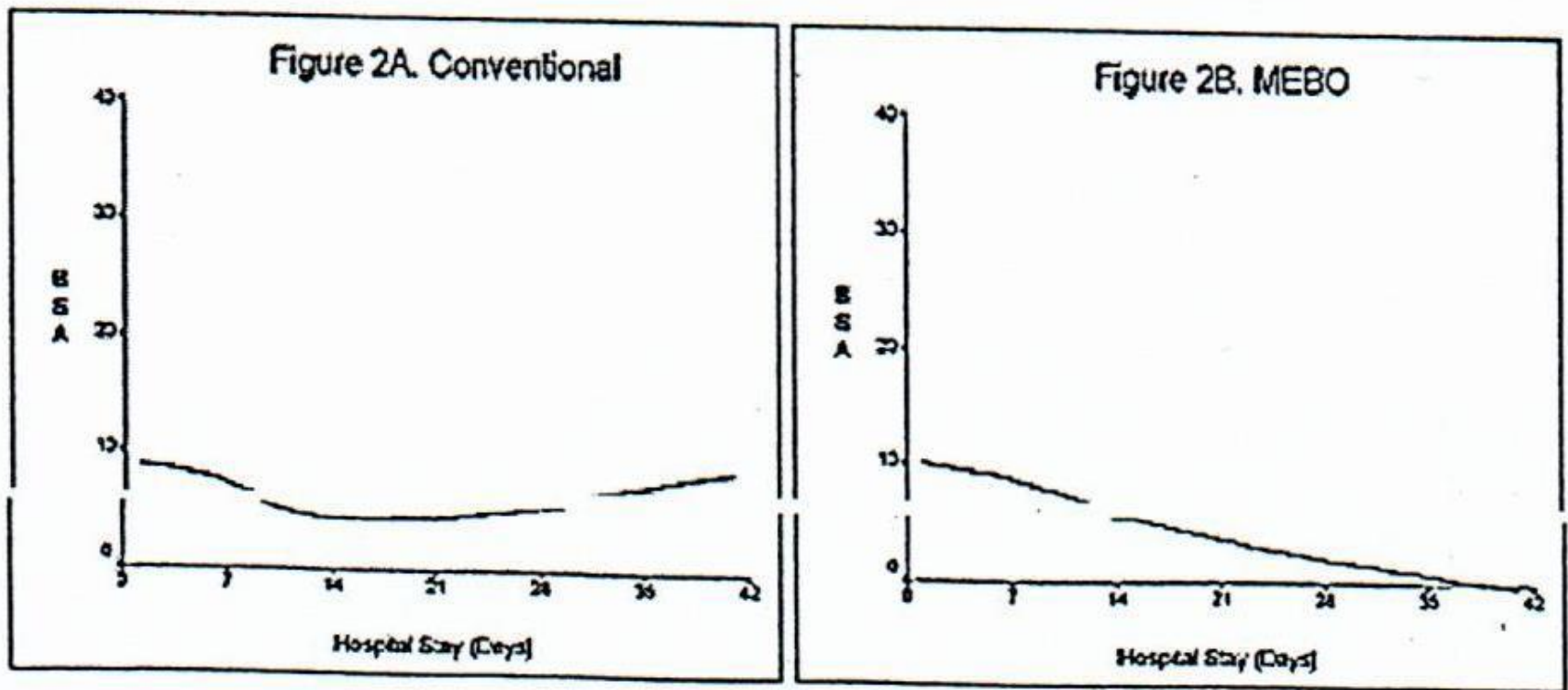
Conventional Dressing

Patients with Second Degree Burns

115 patients randomised

Change in Burn Surface Area (BSA)

Ang, et al (2001)



Statistical Methodology and Associated Software are continually evolving

“Do the above impact on the **studies**
planned several years ago?”

Relook

Ang, et al (2003).

Pain control in a randomized controlled trial comparing Moist Exposed Burn Ointment (MEBO) and conventional methods in patients with partial thickness burns.

Journal of Burn Care and Rehabilitation; 24, 289-296.

What investigators expected of CTERU

Phase II Non-randomised trials
Same Chemotherapy Gemcitabine
Two patient groups

Foo K-F, *et al* (2002). Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. *Annals of Oncology*, **13**, 150-156.

Relook: Gemcitabine: Bayesian Approach

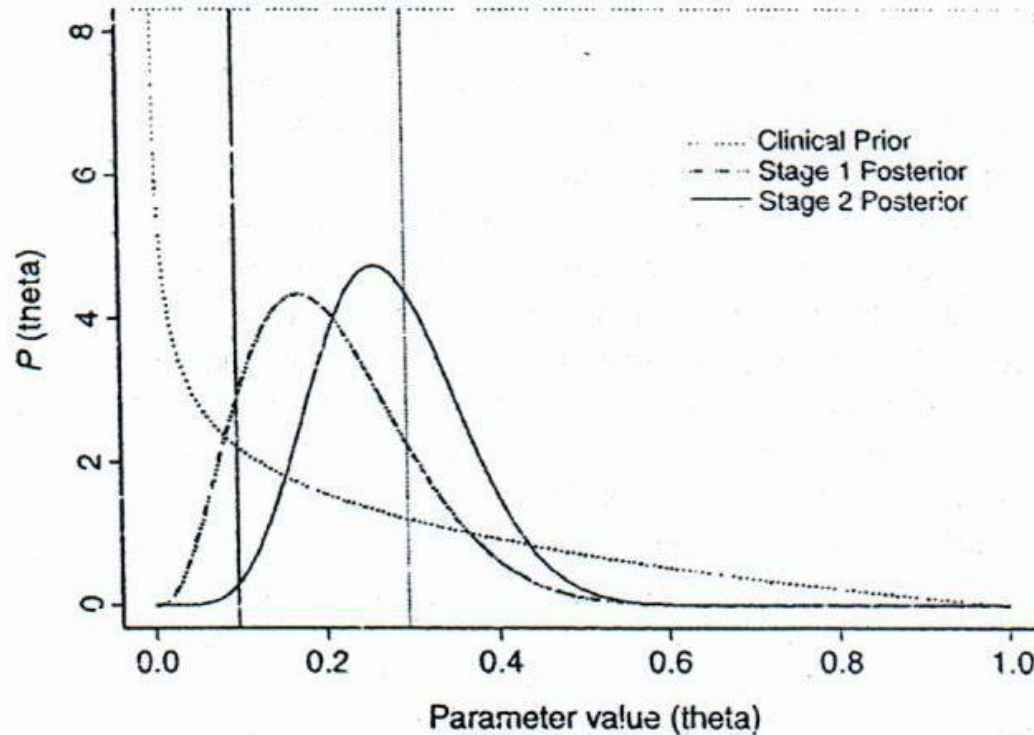


Figure 2 Clinical prior, Stage 1 and Stage 2 posterior for the chemotherapy-naïve group.

More than they expected

Tan S-B, *et al* (2002). A Bayesian re-assessment of two-Phase II trials of gemcitabine in metastatic nasopharyngeal cancer. *British Journal of Cancer*, **86**, 843-850.

NCC: Nasopharyngeal Cancer: Wee J , et al
(2005) Journal of Clinical Oncology, 23, 6730-8

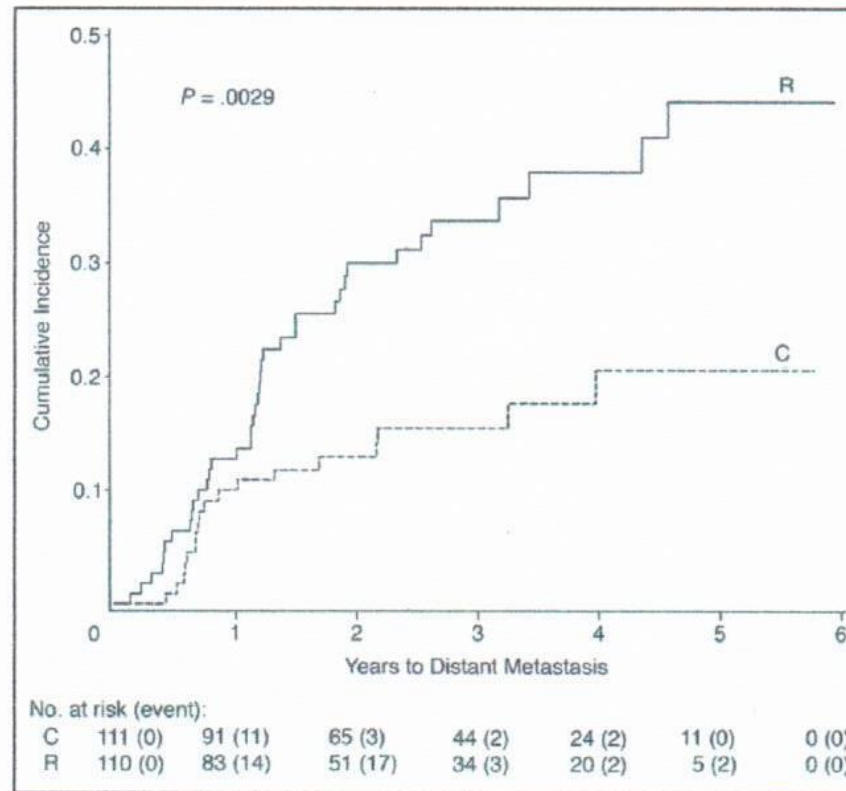


Fig 2. Cumulative incidence of distant metastasis.

6 years later

Tai, Wee, *et al* (2011)

Analysis and design of clinical trials
involving competing risks endpoints.

Trials, **12**, 127

Designing a Confirmatory Trial

Using a Bayesian Methodology?

AHCC03

Lau, *et al* (1999)

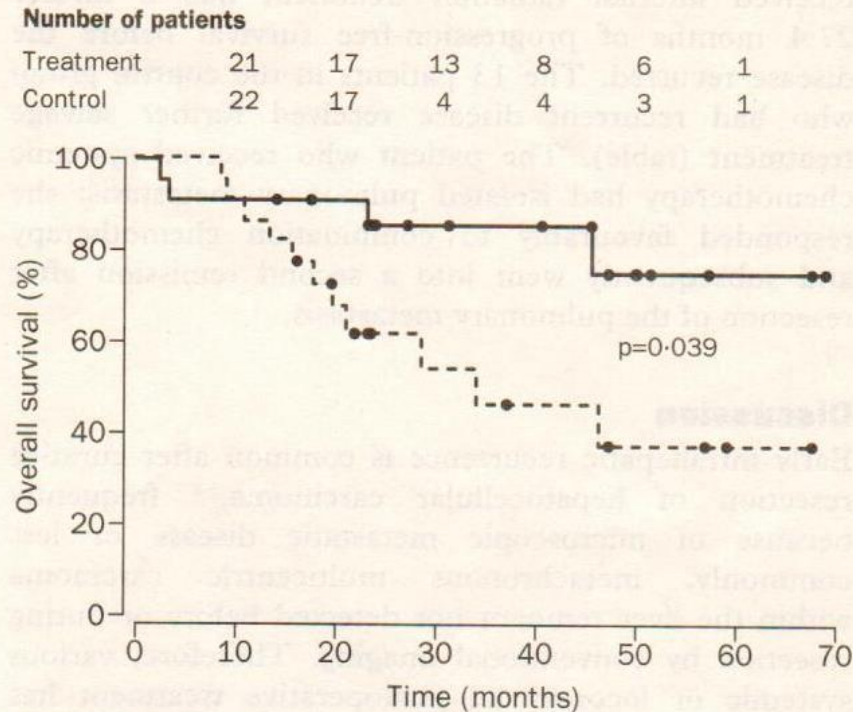


Figure 2: Disease-free and overall survival

Design Stage - Subjective Priors

Tan, Chung, *et al* (2003)

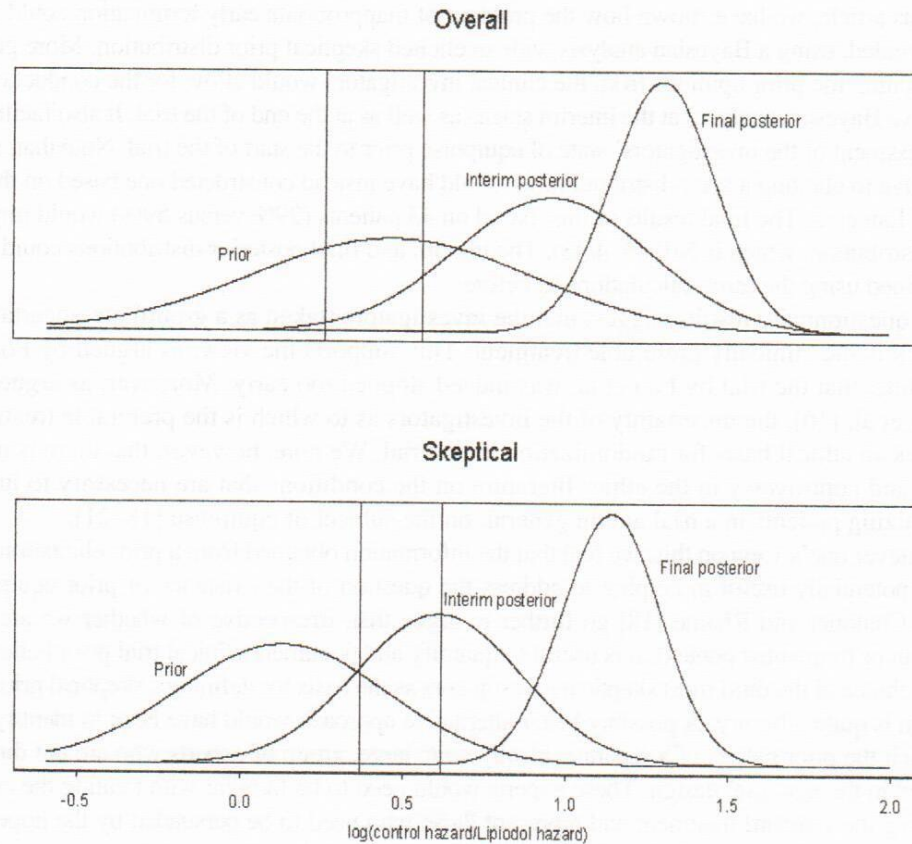
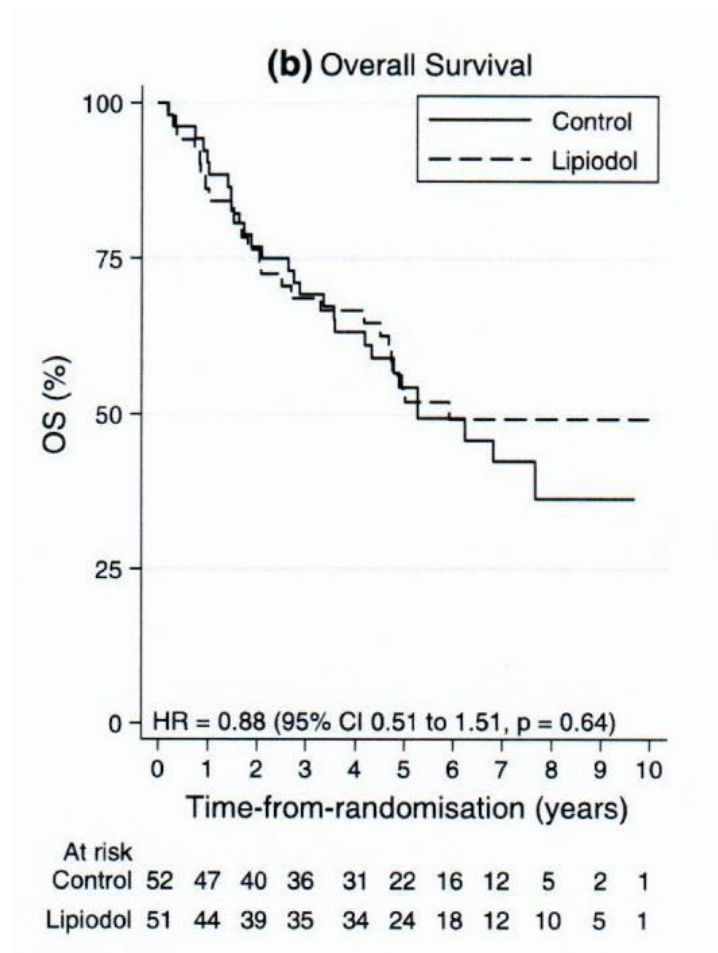


Fig. 3. Prior, interim posterior, and final posterior distributions. Vertical bars indicate range of equivalence.

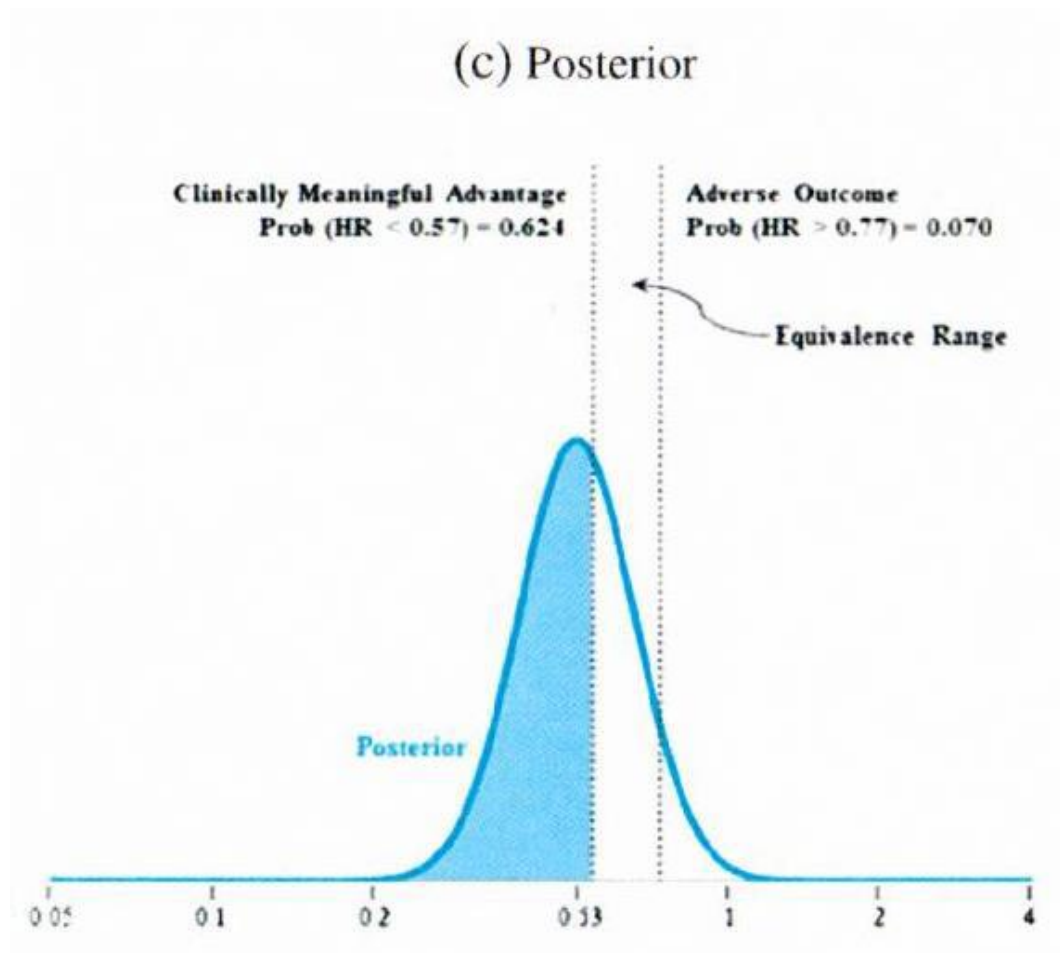
AHCC03 Overall survival

Chung, *et al* (2013) *World Journal of Surgery*



AHCC03

Combining all information available



Role of Iodine accumulated over time?

Gandhi M, *et al* (2015)

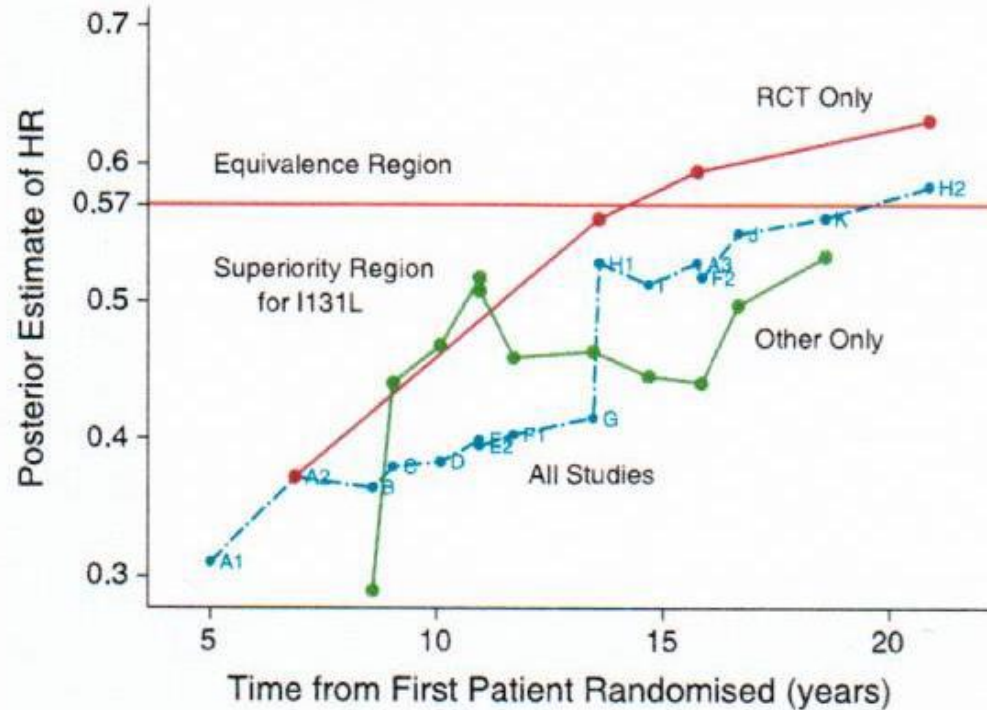
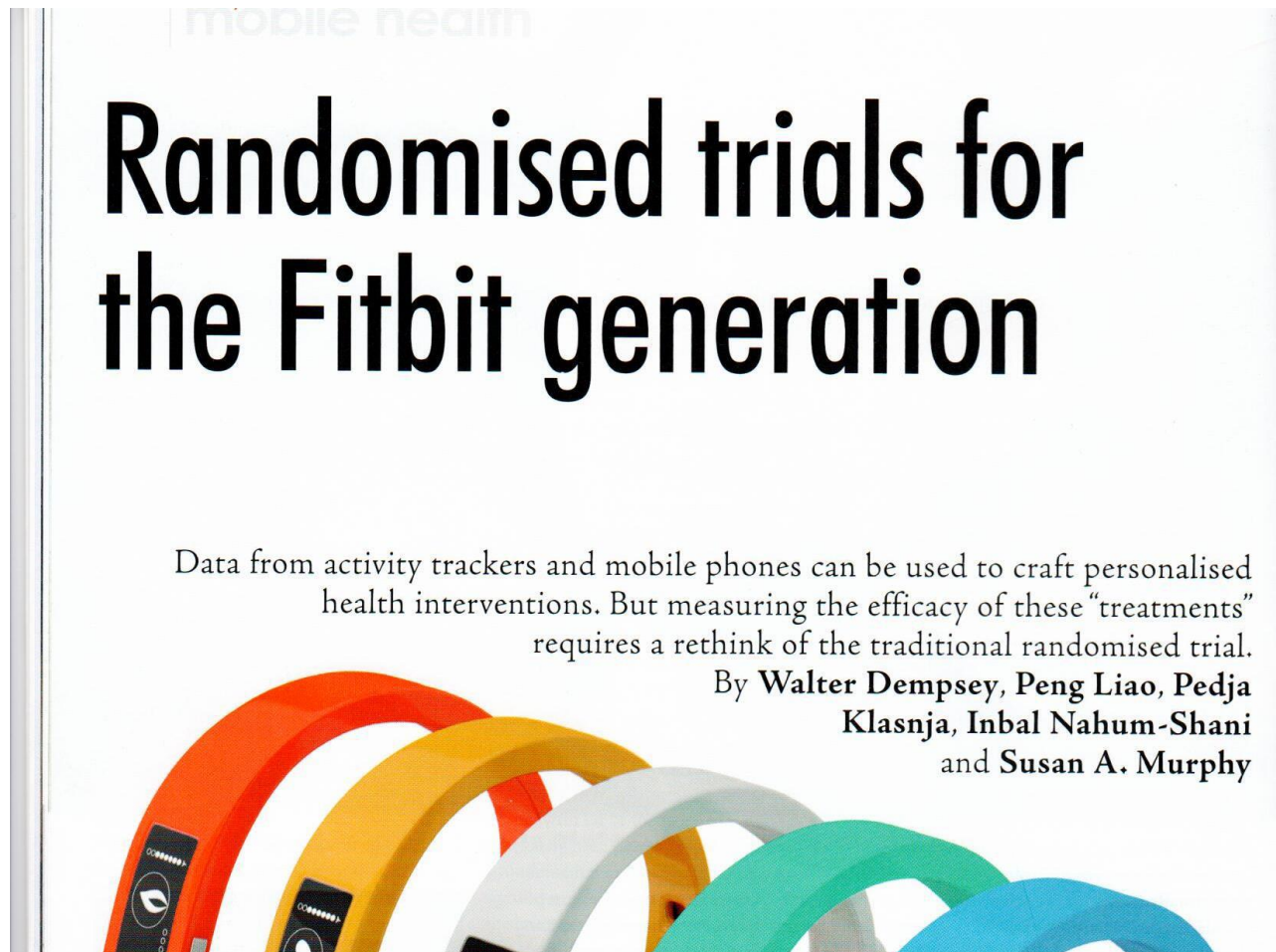


Fig. 3. Evolving posterior HR accumulated from Elements extracted from pertinent studies

Design, Conduct and Reporting of RCTs Intertwines with ever changing Statistical Methodology

What next?



BBC Maxim

“Giving viewers what they want – but better than they expected”

Trials Office Maxim?

“Giving **collaborators** what they want – but better than they expected”