Clinical trials: science vs marketing

Dr Tom Jefferson

Honorary Research Fellow

Centre for Evidence Based Medicine

Oxford OX2 6GG

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Disclosure

- Recipient of a UK NIHR grant for a Cochrane review of neuraminidase inhibitors for influenza (2012-14).
- Royalties from books.
- Occasionally interviewed by market research companies on phase I or II pharmaceutical products.
- 2011-13 expert witness in a litigation case on the antiviral oseltamivir, in two litigitation cases on potential vaccine-related damage and in a labour case on influenza vaccines in healthcare workers in Canada. Retained as a scientific adviser to a legal team acting on oseltamivir (2014).
- Consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013).
- Member of 3 advisory boards for Boerhinger Ingelheim (2014-16).
- Holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews.
- Member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine (2015-16).
- Potential financial conflict of interest on the drug oseltamivir.

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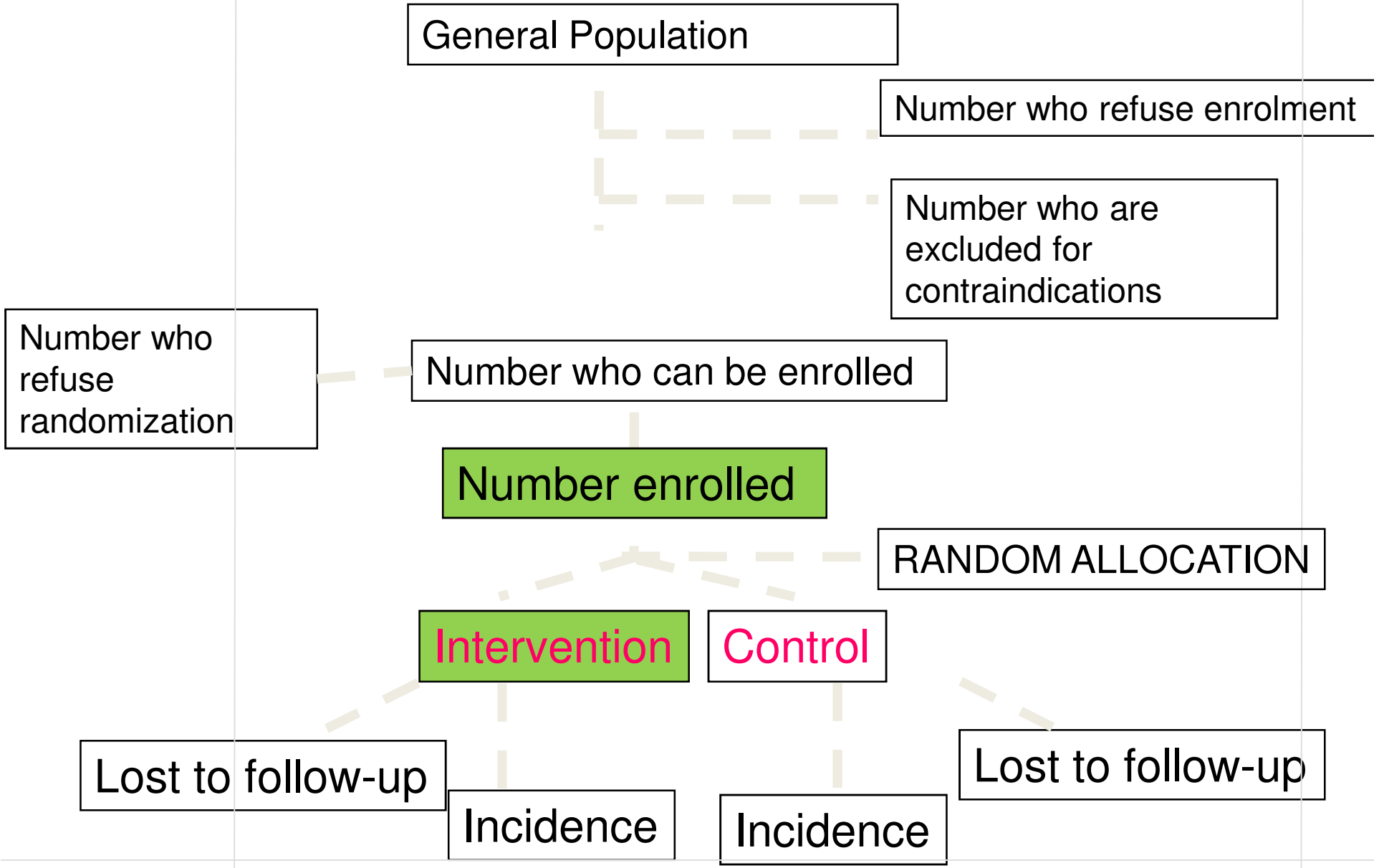
- Why trials are vital
- Key elements of study design
- Some causes of distortion

Why trials are vital

- Best chance of comparing like with like
- Closest we can get to pure experiment
- In a well designed and honestly reported trial any observed differences between arms are most likely to be due to the differences between intervention and control

A hypothetical randomised controlled trial - structure



Key elements of trial design and reporting

- Objective
- Recruitment
- Random allocation
- Choice of comparator(s)
- Blinding
- Follow up

Key elements of trial design and reporting

- Outcome definition
- Measurement
- Analysis
- Summary
- Documentation and Reporting

Causes of distortion

- Poorly worded objective («to confirm..») or shaky rationale
- Recruitment of selected population
- Failed random allocation
- Entry criteria in the analysis population linked with effects of intervention – selection
- If you are worried about harms choose an active comparator
- If you are worried about effectiveness choose a weak comparator

Causes of distortion

- Make interventions identifiably different (blinding failure)
- Change outcome definitions or ways to measure
- Loss of participants at follow up (attrition)
- Restriction of analysis
- Use of Individual Participant Data (IPD) divorced from methods

Causes of distortion

- NEVER lie, but be economical with the truth when needed.
- Control data flow
- Hide a tree? Try a forest

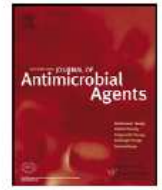
Examples of distortion - Placebo

International Journal of Antimicrobial Agents 35 (2010) 461–467

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag



Safety and pharmacokinetics of oseltamivir at standard and high dosages

R. Dutkowski[a], J.R. Smith[b,*], B.E. Davies[a]

[a] Hoffmann-La Roche Inc., Nutley, NJ, USA
[b] F. Hoffmann-La Roche Ltd., PBMT Bldg 74/3O 104, CH-4070 Basel, Switzerland

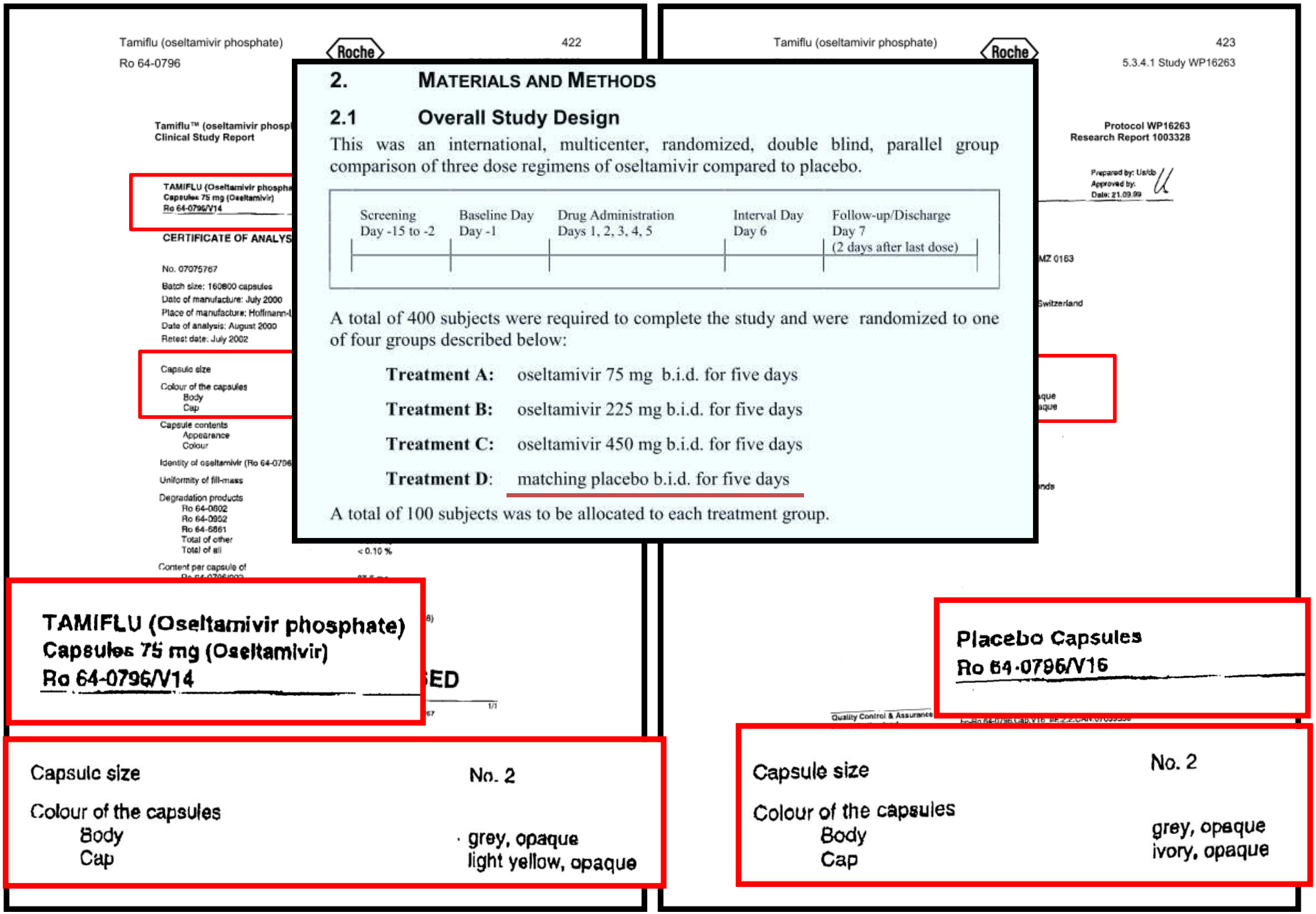
Dutkowski et al 2010

2. Methods

2.1. Study design

This was an international, randomised, multicentre, double-blind, parallel-group comparison with placebo or oral dosages of oseltamivir phosphate of 75, 225 or 450 mg b.i.d. (every 12 h) for 5 days. These dosages were chosen to maximise the likelihood of detection of electrocardiographic changes as well as other adverse effects and were based on the previously observed tolerance of dosages as high as 500 mg b.i.d. in studies in healthy adults [2]. The highest dosage for which blinding could be maintained with available formulations was 450 mg. The study took place between 22 August and 25 September 2000.

Examples of distortion - CERTIFICATE OF ANALYSIS (courtesy of Peter Doshi)



Tamiflu (oseltamivir phosphate)
Ro 64-0796

Roche

422

Tamiflu™ (oseltamivir phosp
Clinical Study Report

TAMIFLU (Oseltamivir phospha
Capsules 75 mg (Oseltamivir)
Ro 64-0796/V14

CERTIFICATE OF ANALYS

No. 07075767

Batch size: 160800 capsules
Date of manufacture: July 2000
Place of manufacture: Hoffmann-L
Date of analysis: August 2000
Retest date: July 2002

Capsule size
Colour of the capsules
Body
Cap
Capsule contents
Appearance
Colour
Identity of oseltamivir (Ro 64-0796
Uniformity of fill-mass
Degradation products
Ro 64-0802
Ro 64-0952
Ro 64-5861
Total of other
Total of all
< 0.10 %
Content per capsule of

2. MATERIALS AND METHODS

2.1 Overall Study Design

This was an international, multicenter, randomized, double blind, parallel group comparison of three dose regimens of oseltamivir compared to placebo.

Screening	Baseline Day	Drug Administration	Interval Day	Follow-up/Discharge
Day -15 to -2	Day -1	Days 1, 2, 3, 4, 5	Day 6	Day 7 (2 days after last dose)

A total of 400 subjects were required to complete the study and were randomized to one of four groups described below:

Treatment A: oseltamivir 75 mg b.i.d. for five days

Treatment B: oseltamivir 225 mg b.i.d. for five days

Treatment C: oseltamivir 450 mg b.i.d. for five days

Treatment D: matching placebo b.i.d. for five days

A total of 100 subjects was to be allocated to each treatment group.

TAMIFLU (Oseltamivir phosphate)
Capsules 75 mg (Oseltamivir)
Ro 64-0796/V14

ED

Capsule size — No. 2

Colour of the capsules
Body — grey, opaque
Cap — light yellow, opaque

Tamiflu (oseltamivir phosphate)

Roche

423

5.3.4.1 Study WP16263

Protocol WP16263
Research Report 1003328

Prepared by: Us/db
Approved by:
Date: 21.09.99

MZ 0163

Switzerland

Placebo Capsules
Ro 64-0796/V16

Quality Control & Assurance

Capsule size — No. 2

Colour of the capsules
Body — grey, opaque
Cap — ivory, opaque

Example – distorted attrition rates

(Source FDA under FOIA 2012-2016)

1121261: FREDERICK G. HAYDEN
CHARLOTTESVILLE, VA 6/7 SIL 9/11 9/13/00 CJC
EXHIBIT 32 page 1 of 4

Revised: October 6, 1997

CONSENT TO PARTICIPATE IN A STUDY

TITLE OF STUDY: A Double-Blind, Randomized, Placebo-Controlled Study of GS4104 (Ro 64-0796) for Prophylaxis Against Human Influenza Virus (HIC#7554)

Payment

You will receive $300 for participating in and completing the study. No payment will be made to you, if you withdraw from the study for personal reasons. An additional payment of $25 will be made each time you are cultured for an influenza type illness. Full payment will be made if you are removed from the study for medical reasons after receiving the study treatment. Other costs such as travel expenses or parking fees resulting from your participation will be your responsibility and are not reimbursable.

n the event that you suffer physical injury directly resulting from the research
n the protocol, no financial compensation for such
vailable. Medical

Trust no one?

Restoring invisible and abandoned trials (RIAT) declaration (from Doshi et al 2013)

Although by definition no journal publication exists for "unpublished trials," clinical study reports for industry funded trials often do exist for these unpublished trials, but they have been traditionally treated as secret