



THE UNIVERSITY OF
MELBOURNE

GCP and its role in clinical trials

APVMA Science Fellows Symposium, 19 April 2010

Prof Ted Whitem
Faculty of Veterinary Science

- The place of Clinical Trials in
 - The drug approval process
 - The practice of veterinary medicine
- The pitfalls of clinical trial evidence
 - Quality of trial design
 - Quality of trial implementation
 - Quality of trial reporting and interpretation
- Overcoming these pitfalls
 - CONSORT
 - REFLECT
 - GCP
- Discussion point – should GCP be required?

- Randomised controlled clinical trials
 - Evaluate efficacy and safety
 - Of the final product
 - For the proposed indication
 - At the proposed labelled dose
 - In the proposed population
 - Are the final component of the Efficacy and Safety evaluation
 - Are relied upon to define label and package insert advice, guidance and warnings

- Randomised controlled clinical trials
 - Provide the data basis for
 - Choice of one product over another
 - Evaluation of potential risks versus benefit

Evidence Based Medicine (EBM) The Evidence Pyramid



<http://library.downstate.edu/EBM2/2100.htm>

- The pitfalls of clinical trial evidence
 - Quality of trial design
 - Quality of trial implementation
 - Quality of trial reporting and interpretation

- Recent Veterinary Attention - Addressed in
 - 1991 at dairy cattle veterinary conference by Chris Baldock for Post Grad Found Uni Syd.
 - 1996 first CONSORT Statement
 - 1999 for evaluation of published clinical trials in veterinary medicine by Whittam at ACVIM 1999
 - 2010 REFLECT derivative of CONSORT first published for Veterinary Clinical Trials

- Addressed in
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CHRIS BALDOCK

CLINICAL TRIALS/

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NEW APPROACHES TO DISEASE INVESTIGATION
AN UPDATE ON CLINICAL TRIALS

Chris Baldock

The advertised title of this presentation conjures up the notion of a broad description of a number of disease investigation methods. I have taken some licence and altered the title and therefore the nature of this presentation somewhat. The following discussion is about one epidemiological method which should be of interest to a wide range of veterinarians involved in dairy cattle medicine and production.

There are plenty of interesting examples of

1935; Cochran and Cox 1957; Mason *et al* 1989). Adaptations of the methods for use in the assessment of disease interventions have evolved from the basic concepts and come under the general title of clinical trials. Again, there are many useful texts on the subject (Friedman *et al* 1985; Fleiss 1986; Meinert and Tonascia 1986) and a number of papers specific to field trials in veterinary medicine (Martin 1978; Chalmers *et al* 1981; Doohoo and Thomas 1989; Martin 1990; Thorburn 1990).

- Addressed in
 - 1996 first CONSORT Statement

JAMA. 1996 Aug 28;276(8):637-9.

Improving the quality of reporting of randomized controlled trials. The CONSORT statement.

[Begg C](#), [Cho M](#), [Eastwood S](#), [Horton R](#), [Moher D](#), [Olkin I](#), [Pitkin R](#), [Rennie D](#), [Schulz KF](#), [Simek D](#), [Stroup DF](#).

From the Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

- Addressed in
 - 1999 for evaluation of published clinical trials in veterinary medicine by Whittem at ACVIM 1999

Criteria for assessment	Reported Yes	Unclear	Omitted No
<i>Introduction</i>			
1 Relevant background			
2 Clear objectives			
3 Properly formulated hypotheses			
<i>Study design and conduct</i>			
4 Animal Use Committee approval			
5 Statistical design described			
6 Appropriate controls			
7 Power calculation – sample size estimates			
8 Good Clinical Practice records – or similar			
9 Reference population defined			
10 Inclusion criteria listed			
11 Exclusion criteria listed			
12 Enrolment before allocation to treatment group			
13 Enrolment with informed consent			

- Addressed in
 - 2010 REFLECT derivative of CONSORT first published for Veterinary Clinical Trials

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Zoonoses and Public Health

ORIGINAL ARTICLE

The REFLECT Statement: Methods and Processes of Creating Reporting Guidelines for Randomized Controlled Trials for Livestock and Food Safety by Modifying the CONSORT Statement[†]


A. M. O'Connor, J. M. Sargeant, I. A. Gardner, J. S. Dickson, M. E. Torrence and Consensus Meeting Participants*: C. E. Dewey, I. R. Dohoo, R. B. Evans, J. T. Gray, M. Greiner, G. Keefe, S. L. Lefebvre, P. S. Morley, A. Ramirez, W. Sischo, D. R. Smith, K. Snedeker, J. Sofos, M. P. Ward and R. Wills

Impacts

- Guidelines for reporting randomized controlled trials should improve the comprehensiveness of reporting.
- Improved reporting should increase readers ability to assess the internal and external validity of study results.
- Improved reporting should increase the potential for study results to be incorporated in decision making.

- Addressed in
 - 2010 the latest CONSORT updates
 - Including commentary about the size of reports for publication, summary and online reports

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ELSEVIER

Journal of Clinical Epidemiology ■ (2010)


**CONSORT 2010 Statement: Updated guide
group randomised tr**

Kenneth F. Schulz^{a,*}, Douglas G. Altma
for the CONSORT Grou

^aFamily Health International, Research Triangle Park,
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^cOttawa Methods Centre, Clinical Epidemiology Program, Ottawa Hospital Rese
and Community Medicine, University of Ottawa, O

Accepted 9 December 2009

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Journal of Clinical Epidemiology ■ (2010) ■

**Journal of
Clinical
Epidemiology**

COMMENTARY

**Updated Consolidated Standards of Reporting Trials (CONSORT):
it just gets better**

Maarten Boers^{*}

Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

Accepted 15 January 2010

In this issue of the *Journal of Clinical Epidemiology*, the Consolidated Standards of Reporting Trials (CONSORT) Group present (insert ref) and elaborate on (insert ref) their updated guidelines. These articles are truly landmark publications, and we should congratulate the group with this

all the proper example text would leave less than 300 words of text specific to their trial. Likewise, a properly worded structured abstract invariably runs beyond the word limit set by many journals.

Hence, although editors declare full endorsement of the

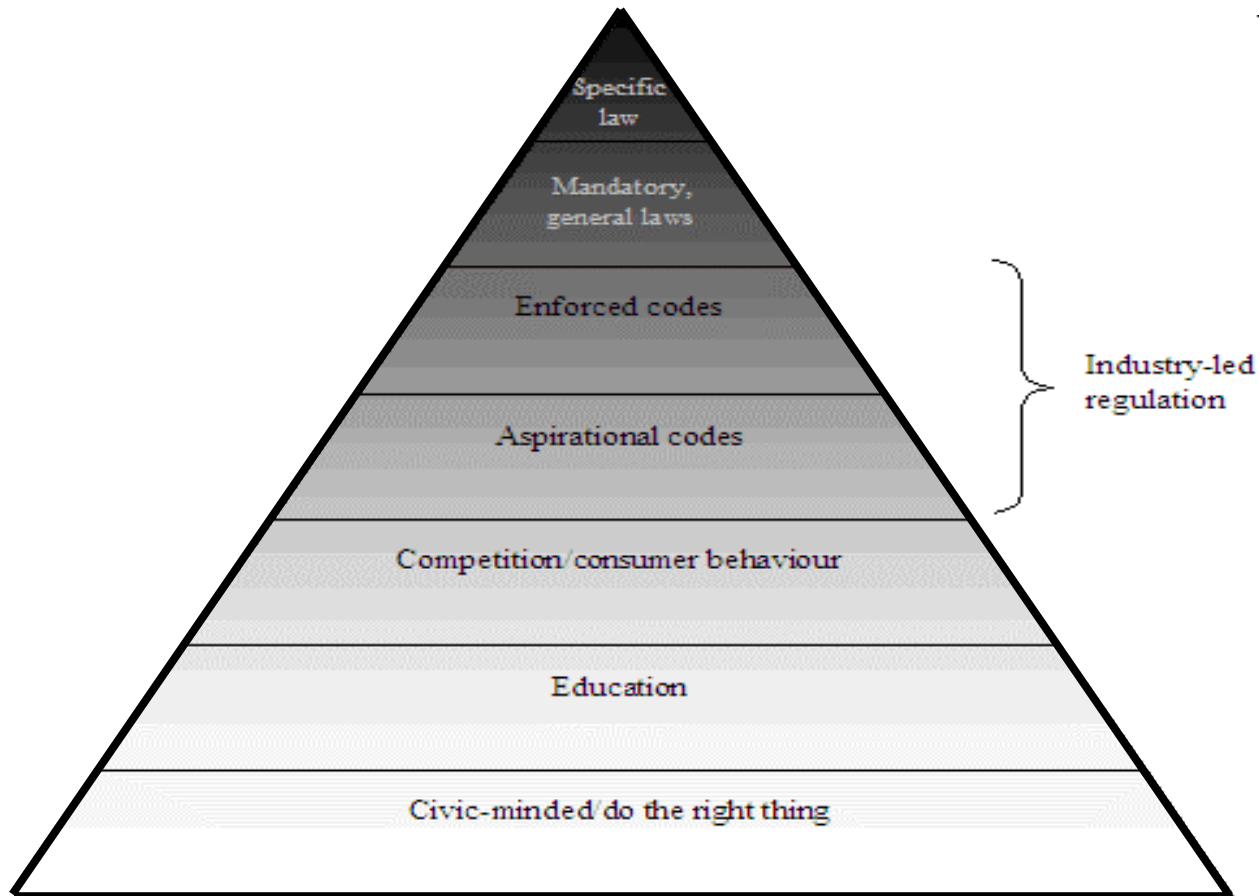
- The pitfalls of clinical trial evidence
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 - Quality of trial reporting and interpretation

Evidence Based Medicine (EBM) The Evidence Pyramid



<http://library.downstate.edu/EBM2/2100.htm>

The Regulatory Pyramid




<http://www.consumeraffairs.govt.nz/policylawresearch/industry-led-regulation/discussion/discussion-03.html>

- GCP

- The European Agency for the Evaluation of Medicinal Products *Veterinary Medicines and Information Technology Unit CVMP/@101/595/98-FINAL* London, 4 July 2000
VICH Topic GL9 (GCP) Step 7 Consensus Guideline
GUIDELINE ON GOOD CLINICAL PRACTICES
- http://www.vichsec.org/pdf/2000/GI09_st7.pdf
- “Good Clinical Practice is intended to be an international ethical and scientific quality standard for designing, conducting, monitoring, recording, auditing, analyzing and reporting clinical studies evaluating veterinary products. *Compliance with this standard provides public assurance about the integrity of the clinical study data**, and that due regard has been given to animal welfare and protection of the personnel involved in the study, the environment and the human and animal food chains.”
**emphasis added*

- GCP
 - “A standard for the design, conduct, monitoring, recording, auditing, analysis, and reporting of clinical studies. *Adherence to the standard provides assurance that the data and reported results are complete, correct and accurate**, that the welfare of the study animals and the safety of the study personnel involved in the study are ensured, and that the environment and the human and animal food chains are protected.”
**emphasis added*

- GCP
 - Is required for the registration of veterinary products in the EU, USA, Japan and Canada
 - Is not (currently?) required in Australia
 - But is referred to on the APVMA website
 - Australia is an observer to the VICH and is encouraged to implement VICH recommendations

- GCP
 - aims to reduce the incidence of factors that may be associated with incorrect regulatory decisions
 - Fraud
 - Misconduct
 - Misrepresentation
 - Omission
 - Carelessness
- 

- Audits for compliance with GCP
 - Aim to identify
 - Are source data accurate?
 - Are source data complete?
 - Exactly who recorded the source data?
 - Have/Can the source data been/be altered?
 - Were the data collected in the correct sequence?
 - Are ALL the data considered in the Final Report?
 - Do the data support the conclusions that have been drawn?

- With or without GCP
 - The APVMA (and other regulators) rely upon the Sponsor or their CRO to ensure the validity, quality, and credibility of the data.
 - Because fraud, misconduct and carelessness remain frequent, even in territories with GCP requirements, regulators like the FDA and CVMP are increasing their focus on GCP compliance.

- The advantages of GCP
 - Global acceptance of the data
 - Particularly important for companion animal IVPs
 - Building credibility with APVMA
 - Better assurance for the Sponsor of value for money from CRO's
 - Complete records for later review & re-use
 - Better reproducibility (SOPs, Templates, etc) when replicating with similar studies

- The key components of GCP
 - Well trained personnel
 - Investigators, monitors, auditors
 - Well prepared and completed documents
 - Protocols, Case record forms, SOPs, Report Templates, Training Records, Communication logs
 - Contracts with CRO
 - Make sure the necessary detail is in the contract

Transfer of responsibilities of Sponsor to CRO.

Responsibilities of Sponsor

1. Selection of investigators
2. Qualification and training of investigators
3. Providing investigators with necessary information to enable proper conduct of the study
4. Ensuring that the protocol conforms to VICH GL9 (GCP) (June 2000) protocol requirements
5. Ensuring the study is conducted according to the protocol
6. Ensuring that the study is conducted and reported to conform with VICH GL9 (GCP) (June 2000) protocol requirements
7. Prompt reporting to the sponsor of any and all adverse reactions that occur during the study
8. Ensuring that all test article is accounted for
9. Obligation to appoint auditors and monitor/s

- The key components of GCP
 - Well trained personnel
 - Investigators, monitors, auditors
 - Well prepared and completed documents
 - Protocols, Case record forms, SOPs, Report Templates, Training Records, Communication logs
 - Contracts with CRO
 - AEC approvals, Owner consent forms
 - Everything ordered, filed, catalogued and easy to retrieve

- GCP for Australian-based studies?
 - Global acceptance of the data
 - Particularly important for companion animal IVPs

What are the ramifications?

- Compliance Inspection
 - If you submit an Australian-based GCP study for a NADA in the USA you are very likely to be inspected
 - Your FDA inspector will review
 - The whole of the Regulatory Binder – in overview
 - A selection of case files
 - » Some from early, middle and late in the study
 - » These cases selected will have 100% review
 - 100% of owner consent forms
 - All adverse events
 - IVP inventory for all study sites (100% review)
 - All deviations and amendments

- Compliance Inspection
 - If you submit an Australian-based GCP study for a NADA in the USA you are very likely to be inspected
 - You might have a ‘targeted’ inspection
 - if the preliminary desk audit of the regulatory binder identifies potential problems or
 - if the efficacy or safety reviewers at the CVM have targeted questions about the data or a possible study site effect

- Compliance Inspection
 - Do your records confirm each of the following?...
 - That the animals
 - actually exist
 - satisfy the enrolment criteria
 - » They have the target disease
 - should not have been excluded
 - » Other conditions, confounding treatments, etc
 - Was owner consent obtained for every animal prior to its enrolment?
 - sequence of records is important
 - Was AEC approval obtained?

- **Compliance Inspection**
 - Do your records confirm each of the following?...
 - Were there protocol amendments or deviations?
 - Are these correctly recorded?
 - Were all the AEs reported?
 - Are you trying to hide something?
 - Is there evidence of Fraud?
 - Case Records are original?
 - Case acquisition rates do not markedly vary without adequate explanation in the communication logs?
 - Were there any drop-outs?
 - Are they correctly documented and reported?
 - Is there appropriate follow up

- Compliance Inspection
 - The inspector will also pay close attention to
 - Monitors and Clinical Research Assistants
 - Training
 - Frequency of visits
 - Records
 - » E.g. make sure the vehicle mileage reports correspond to the distance travelled to the investigator site on the appropriate day
 - » E.g. make sure telephone, fax, mail and email correspondence is all filed in chronological order and that the records at each end of the conversation 'align'
 - Monitor Reports to management (Sponsor)
 - Monitor Reports to Investigator
 - » And the Investigators' response

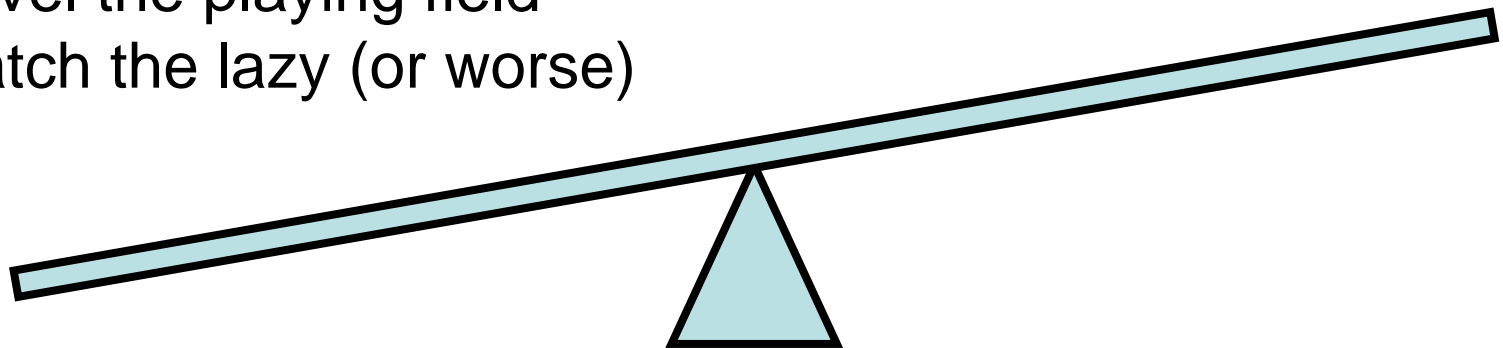
- **Compliance Inspection**
 - The inspector will also pay close attention to
 - Records of ‘test runs’ of the protocol – e.g. training cases
 - These must be part of the Study Binder
 - Records of the randomisation and masking processes
 - IQ/OQ of computer hardware and software
 - Validation of spreadsheets and data entry
 - Contracts between Sponsor and CRO
 - Are delegations of Sponsor authorities correctly made?

- Compliance Inspection
 - The inspector will also inspect a sample of your investigator sites
 - Are they still in business?
 - Who has the ORIGINAL records?
 - Did the Investigators keep all their records?
 - Do their records match the Sponsor's?

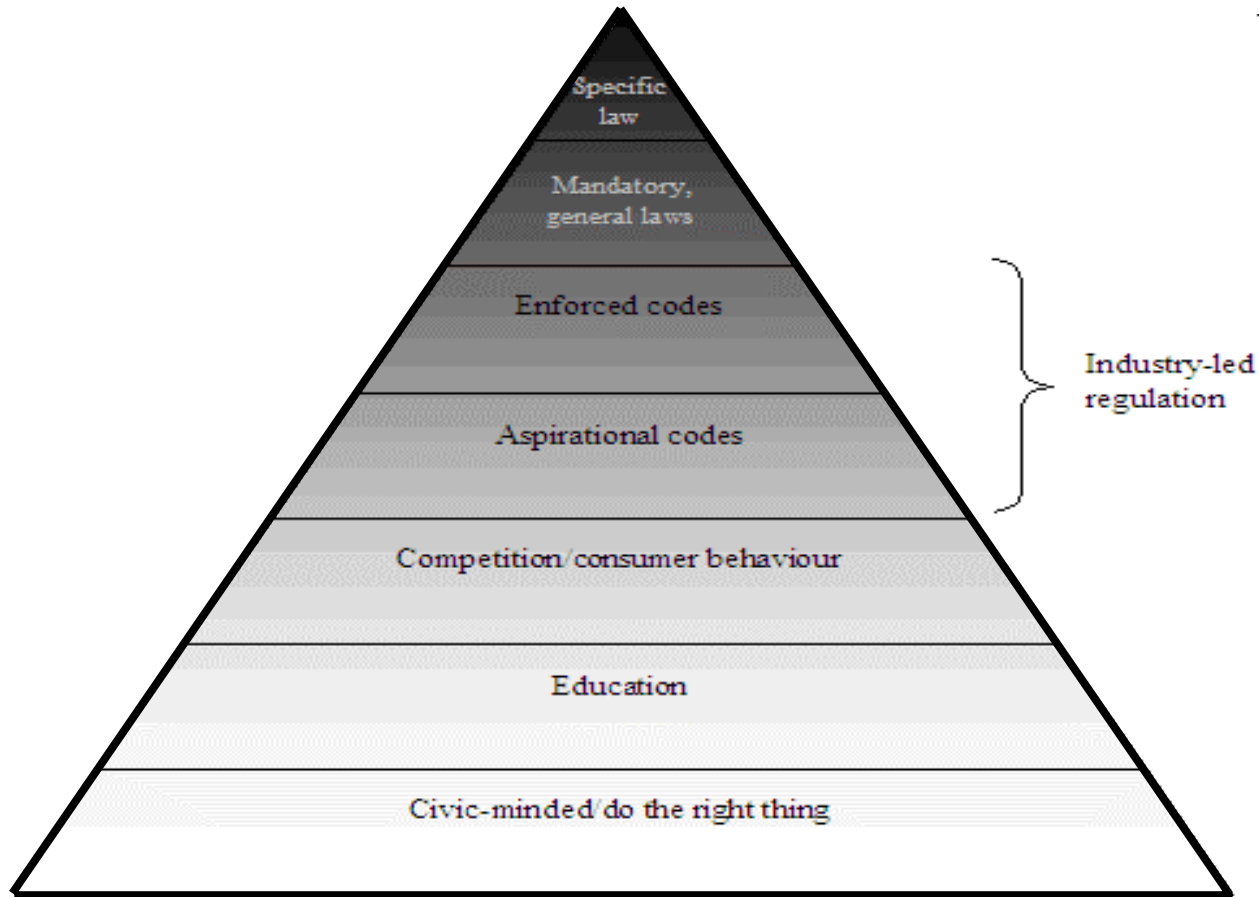
- Compliance Inspection
 - Should the APVMA conduct audit inspections for clinical trials conducted in Australia?
 - Some Sponsors
 - are not familiar with GCP
 - do not claim to adherence to GCP
 - have no track record of GCP compliance
 - use GCP sometimes and not other times
 - \$\$\$
 - How would such a compliance inspection program be funded?

- Should APVMA require GCP?

- | | |
|-------------------------------|-----------------------------|
| ✓ Improve study quality | ✗ More staff needed |
| ✓ Improve ease of review | ✗ Increase paperwork |
| ✓ Improve speed of review | ✗ Increase compliance costs |
| ✓ Increase public confidence | ✗ Slower development times |
| ✓ Reputational impact at VICH | |
| ✓ Level the playing field | |
| ✓ Catch the lazy (or worse) | |



The Regulatory Pyramid



<http://www.consumeraffairs.govt.nz/policylawresearch/industry-led-regulation/discussion/discussion-03.html>



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