The Evolution of Clinical Trial Transparency (Registries)

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Publication bias - concerns

- How do we know if all studies are published?
- Do publications accurately reflect the conduct of studies?

Protocol registration

- Pioneered by ICMJE, WHO and others
- Enables studies to be tracked to publication
- Enables review of submitted manuscripts against the protocol summary
- Helps reduce duplication
- Provides opportunities for participation

Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors

Publication bias - concerns

- How do we know if all studies are published?
- Do publications accurately reflect the conduct of studies?
- **What happens when a study is not published in a peer-reviewed journal?**

Results registration

- Pioneered by industry
- Results in the public domain irrespective of outcome and whether or not studies are accepted for publication

GSK Clinical Study Register Launched October 2004

Lilly Clinical Trials Launched December 2004

Providing access to protocol and result summaries

Current GSK Approach – Posting on Registers and Databases

Protocol summaries and result summaries posted for:
- Clinical trials (phase I-IV)
- Observational studies that evaluate medicines
- Meta-analyses that evaluate medicines
- Results posted:
  - At the time of approval
  - Within 12 months of termination
  - Within 12 months of LSLV for phase IV studies

Posting Clinical Study Information

2010 = 4069

What Information is Posted?

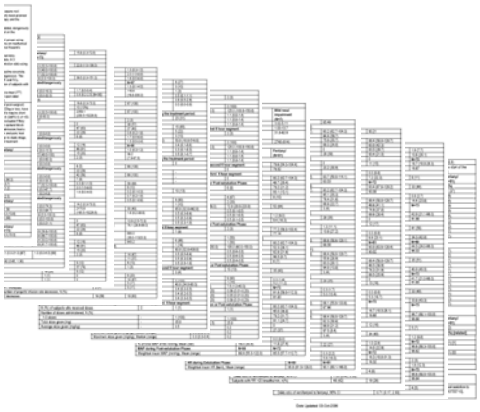
Pre-determined scientific non-promotional information.

- Study title/rationale/objectives/phase
- Study design/treatment schedule/location(s)
- Statistical methods
- Study period
- Study population/demographics
- Results for primary and secondary endpoints defined in the trial protocol
- Adverse events (including all serious adverse events)
- Names of principle investigators
- References to publications in the medical literature

What Does it Look Like?

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: USA30206
Title: A randomised, double-blind, parallel group, multi-centre study comparing the safety and efficacy of a remifentanil and propofol regimen versus a fentanyl and propofol regimen, including an investigation of the pharmacokinetics of remifentanil and remifentanil acid, in Intensive Care Unit patients requiring analgesia and sedation in association with short-term mechanical ventilation.
Rationale: It was proposed that a remifentanil-based treatment regimen could offer advantages over a standard analgesia and sedation regimen for subjects in the Intensive Care Unit (ICU).
Phase: III
Study Period: 12 July 1999 to 19 June 2000
Study Design: A randomised, double-blind, parallel group study. There were 3 phases: open-label randomised pilot phase; open-label practice phase; and randomised double-blind phase.
Centres: 21 centres in 5 countries (Germany [8], Spain [4], United Kingdom [4], Belgium [4] and The Netherlands [1])
Indication: Analgesia and sedation in critically ill patients
Treatment: For all subjects the study was divided into 4 periods: Screening: from ICU entry until starting study drug intravenous infusion Treatment: from starting until stopping study drug opioid infusion (maximum of 72 hours treatment and 1 hour weaning). During the maintenance phase (from starting study drug until starting extubation), subjects in the double-blind phase received study drug at a starting infusion rate of 6ml/h (remifentanil 9microg/kg/h [0.15microg/kg/min], fentanyl 1.5microg/kg/h [0.025microg/kg/min]), which was titrated using a pre-defined algorithm to a target Sedation Agitation Scale (SAS) score of 4 (subject was calm and co-operative) with no or mild pain. If and when the opioid infusion rate reached 8ml/h (remifentanil 12microg/kg/h, fentanyl 2microg/kg/h), any requirement for additional sedation was provided by a bolus dose of propofol (up to 0.5mg/kg) and the initiation of a propofol infusion at a starting rate of 0.5mg/kg/h. During the extubation phase (from starting the extubation process until subjects was extubated), propofol infusion was stopped and study drug infusion was reduced to 4ml/h over a period of up to 1 hour. Open-label sedation (propofol) and analgesia (fentanyl) were used. Post-extubation, study drug was reduced by 25% of the rate at the start of extubation and then by 25% decrements at 20 minute intervals. Open-label sedation (propofol) and analgesia (fentanyl) were used. Post-treatment: from stopping study drug until 24 hours later, ICU discharge, or death which ever occurred first. Follow-up: from 24 hours after stopping study drug until ICU discharge, end of Day 7 after entering the ICU or death, whichever came first.
Objectives: to compare the effectiveness of the remifentanil and propofol regimen with the fentanyl and propofol regimen in terms of the level of sedation provided and the doses of opioid and propofol required; to compare the adverse event (AE) and haemodynamic profile of the 2 treatment regimens; and to examine the pharmacokinetic (PK) profile of remifentanil and remifentanil acid in subjects with normal renal function and mild renal impairment.
Primary Outcome/Efficacy Variable: The between-subject variability around the mean percentage of hours of optimal sedation (defined as a SAS score of 4), evaluated from the start of study drug infusion until either start of extubation or 72 hours after the start of study drug infusion (whichever came first).
Secondary Outcome/Efficacy Variable(s): Mean percentage of hours subjects were optimally sedated (SAS=4), inadequately sedated (SAS=5, 6 or 7), excessively sedated (SAS=1,2 or 3), dangerously agitated (SAS=7) or unrousable (SAS=1); mean percentage of hours with no/mild pain during the treatment and post-treatment periods; time between start of extubation and actual extubation; total time on mechanical ventilation within the treatment period; time between extubation and ICU discharge; time from start of the study until ICU discharge. Other secondary efficacy endpoints were: weighted mean infusion rates of remifentanil, fentanyl, and propofol; total exposure to study opioid and propofol including frequency of opioid infusion rate changes and propofol infusion rate changes (from starting the opioid infusion until it was discontinued); incidence of supplementary open-label propofol and fentanyl bolus doses administered for stimulating procedures during the Treatment Period; incidence of open-label propofol and fentanyl bolus doses administered for rescue treatment during the Maintenance Phase; incidence of supplementary open-label propofol, fentanyl, morphine and bupivacaine bolus doses administered for analgesia/sedation during the Extubation and Post-Extubation Phases. PK secondary endpoints included remifentanil and remifentanil acid blood concentrations. Safety endpoints were: haemodynamic parameters during and after treatment (mean arterial pressure [MAP] and heart rate [HR]); respiratory function (post-extubation only- respiratory rate [RR], fractional inspired oxygen concentration [FiO2] and peripheral oxygen saturation [SpO2]), incidence of adverse events.



Current GSK Approach – Publication in the Scientific Literature

Discovery → Development → Regulatory Review → HTA and Reimbursement → Patient Access, Research

Commitment to seek peer-reviewed publication **AS MANUSCRIPTS** of all:

- Clinical trials (phase I-IV)
- Observational studies that evaluate medicines
- Meta-analyses that evaluate medicines
- Submission within:
  - 12 months of approval
  - 12 months of termination
  - 18 months of LSLV for phase IV studies
- Should publication not be possible, context and interpretation will be added to the result summary on our register

Where next?

We don't have all the answers.

We welcome dialogue and constructive discussion with stakeholders.

Study Results Posting for Patient Benefit

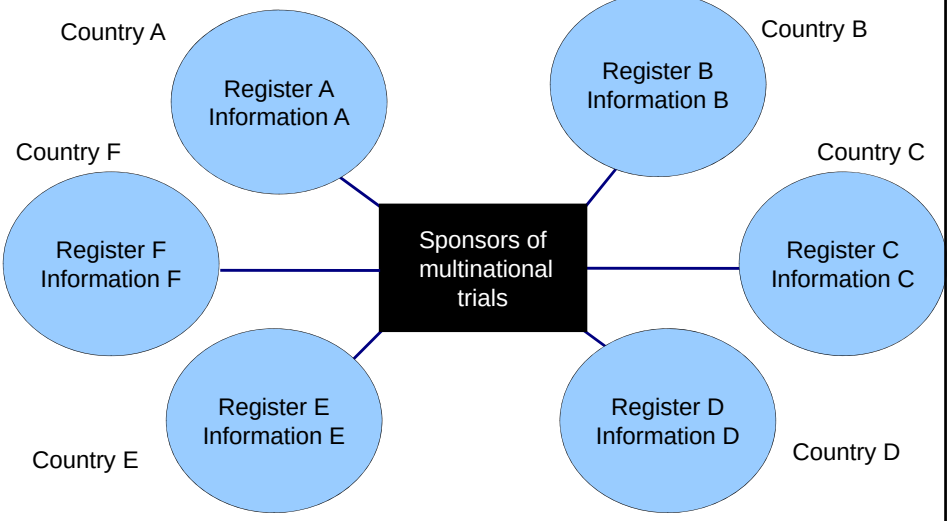
Audiences that use Results Posted on Registers

- Academic researchers
- Meta-analysts
- Journal editors
- Third party payers
- Lawyers
- **Healthcare practitioners?**
- **Patients?**

Uses

- To conduct meta-analyses and reviews
- Re-analyze individual study data
- By industry to inform clinical programs
- By editors when reviewing manuscripts
- **Guide/inform treatment decisions at the physician and patient levels?**

Need for harmonisation



Timing of Disclosure

European Commission has issued a Communication that would require the public disclosure of results from phase II-IV clinical trials with 12 months of completion of the trial irrespective of the approval status of the medicine.

In the US, the FDA Amendments Act (FDAAA) includes language regarding the potential for study results posting for unapproved products at some point in the future

Getting the balance right for patient benefit

Study Results Posting: Interpretative (Lay) Summaries

- Title VIII of the FDA Amendments Act stipulates that not more than 3 years after enactment the HHS Secretary will expand the NIH study results database by rulemaking to provide:

  "A summary of the clinical trial and its results that is written in non-technical, *understandable language for patients,* if the Secretary determines that such types of summary can be included *without being misleading or promotional."*

- Public meetings held in 2009
  - Determine need
  - Identify a process for producing summaries

Interpretative (Lay) Summaries
Key Issues to be Addressed

- Determining need
  - NEJM was not supportive because of the authorship issues
  - Others (e.g. Consumer's Union) felt they were critical
- Authorship
  - How can we ensure they are non-promotional and accurate?
  - How can we ensure they are understandable –reading level?
  - Who will write the summaries? – Independent writing groups?
  - Who will review the summaries? – Regulators?
  - Who will pay for writing and review?

Summary

Current Approach → Future Challenges

Audiences for postings and publications

Need for harmonisation

Timing of disclosure

Posting interpretative (lay) summaries