

# Let's Standardize Reporting of Clinical Trial Results! – A Patient Advocate's Perspective

*An Opportunity to Improve Public Understanding and Trust in Clinical Research, while Making Analysis by Experts More Efficient*

Reporting bias represents a major problem in the assessment of health care interventions.<sup>1</sup> Here we note that the lack of standards on what needs to be reported and how it is formatted contributes to reporting bias, the misunderstanding of published results, difficulty in finding and comparing results, which sometimes contributes to mistrust in clinical research.

Pick a clinical abstract at random and you may get a feel for how challenging it to extract the key information and its significance:

Information is organized in a random order, and selected by the authors

Here we propose the use of required elements and a tabular format for reporting on clinical trials for interventions against cancers and perhaps other life-threatening conditions – which we expect could be complementary to the National Institutes of Health goal to expand the Clinical Trials Registry and Results Database.<sup>2</sup>

| Elements                            | TELL Report Format (proposed starting point):   |
|-------------------------------------|---|
| <b>N</b>                            | Number of participants in the clinical trials - Evaluated / Intent to Treat.  |
| <b>Evaluated / Intent to Treat</b>  | We propose that intent to treat be included in all clinical research abstracts, expressed as:<br>N = Evaluated /ITT, Example: Evaluated: N = 300/500  |
| <b>Population</b>                   | Medical condition (and subtypes):<br>Risk: High, medium, low risk<br>Performance Index   Prognostic Index   |
| <b>Clinical circumstance</b>        | Median number of prior therapies (and type)<br>Median age   Genetic characteristics if any  |
| <b>Study Type</b>                   | Phase:<br>Randomized / Single arm<br>Prospective / Subtype analysis   |
| <b>Primary Clinical Questions</b>   | Endpoints:<br>Safety   Overall response rate   CR rate, Progression Free Survival,   Survival ...   |
| <b>Primary Findings</b>             | As defined in Primary Clinical Questions<br>Expressed as Rate, include Confidence range, such as:<br>Evaluated: CR/n (%) (CI range)<br>Intent to Treat: CR/n (%) (CI range)<br>Safety   Overall response rate   CR rate, Progression Free Survival,   Survival ...<br>Provide pre-specified goal (relative to historical control) if a single-arm study |
| <b>Secondary Clinical Questions</b> | Provide pre-specified goal (relative to historical control) if a single-arm study   |
| <b>Secondary Findings</b>           | As defined in Secondary Clinical Questions<br>Expressed as Rate, include Confidence range, such as:<br>Evaluated: CR/n (%) (CI range)<br>Intent to Treat: CR/n (%) (CI range)<br>Median follow-up:  |
| <b>Follow-up</b>                    | Final or Next:  |
| <b>Administration</b>               | How protocol was scheduled and administered<br>Cycle = X, Number of Cycles,<br>Number of Treatment Days, Treatment Duration in weeks<br>Route: Oral, IV, Continuous Infusion, Subcutaneous  |
| <b>How Endpoints were measured</b>  | Summary of how outcomes were measured, such as:<br>By: Independent / Investigator<br>Schedule (weekly, monthly):<br>Type (blood, imaging):  |
| <b>Maturaton of Data</b>            | Completed / Intermitt?<br>Time to enrollment and analysis?<br>Median time of follow up,<br>Need for follow-up?  |
| <b>Safety Results</b>               | Expressed as rate with range:<br>By Grade (severity): Serious first,<br>For Evaluated: SE/n (%) (CI range)<br>For ITT - if toxicities led to dropping out   |
| <b>Mortality</b>                    | Death rate: Treatment-related, Other:<br>On study   Off Study<br>Evaluated   Intent to Treat  |
| <b>Limitations</b>                  | Expected rate in this population:<br>Authors describe limitations of the study methods and design - such as sample size, or study type ... to describe level of evidence and if findings are consistent with other studies  |
| <b>Discussion</b>                   | Free text area. Authors might provide here the implications of the findings - interpretations, and background that does not fit in the clinical results fields.   |

Information is organized logically as determined by peer review

Scientists may argue that the intended audience for clinical research is not the patient community or the public at large – that clinical abstracts are informal summaries (conversations) by and for scientists and that structured reporting would be burdensome. We remind that by definition clinical research requires patient participation – involves individuals who take substantial risks

<sup>1</sup> Natalie McGauran, et; **Reporting bias in medical research - a narrative review** ; Trials. 2010; 11: 37. 2010 April 13. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2867979/>

<sup>2</sup> NIH: **Expansion of the Clinical Trials Registry and Results Data Bank** <http://grants.nih.gov/grants/guide/notice-files/not-od-09-077.html>

when participating in drug trials; and that improving patient outcomes is the core objective of clinical research.

We note also that there are many hidden costs, inefficiencies, and missed opportunities associated with free-form clinical reporting, including an invitation for biased reporting – by what is left out, over-emphasized, or lost in the clutter.

*"Ethical clinical research should contribute to generalizable knowledge and improve human health. The dedication of patients who take the risks to participate in clinical research is dishonored when their data remain secret."* - Alastair J.J. Wood, M.D.<sup>3</sup>

We are compelled to add to Dr. Wood's comment that patients are short-changed in more subtle ways when the data is obscured or biased, even if unintentionally by how it is presented and then misinterpreted by the various stakeholders. The **media** – tending to report in ways that attract readers, or the **drug sponsors** – tending to report in ways that attract investors, or the **investigators** – tending to report in ways that will support their hypothesis or enhances the significance of their work or invention. This is not to suggest that evil intent or deliberate calculations to deceive are guiding the actions of investigators or drug sponsors, who truly play vital roles in clinical research.

Most patients when initially diagnosed with a cancer have little or no medical background or training in drug assessments or scientific method. Nor do we often have access to the full text of reports published in medical journals. However, the abstracts describing this research are widely available on the Internet or indirectly reported through press releases, which have a very poor track record for objective reporting.<sup>4</sup>

The review of clinical reports is a complex task that requires extensive training and skill. However, many patients facing life-threatening disease, or their loved ones, have an urgent need to know – will often do their best to uncover what the studies suggest or seem to prove in order to make more informed clinical decisions.

Faced with media-born misinformation and conflicting interpretations even among professionals, the public may lose trust in the clinical research process. Lacking standards for reporting, patient and physician analysis will be based often on incomplete information. The beliefs of patients will be based on happenstance – acquired from untrained parents, an influential friend, the claims made in shock media, a best-selling book or popular website – which makes the goal of informed medical decision-making more challenging than it needs to be. Amid the chaotic reporting standards we have observed that one report can be, unwisely, considered equivalent to any other by patients and sometimes patient advocate groups. That is, patients may trust specific clinical trial reports too much or too little, or embrace them too selectively ... based on what we want to be true, or based on the faith we have in certain individuals or institutions – or we may unwisely mistrust any study funded by a drug company or the government.

To help to address the confusion and its associated costs, we ask if a structured format could be required for clinical reports submitted to the medical journals – with a focus on the elements of clinical research that are key to assessment of any drug by the FDA for marketing approval. Noting that one need not have a deep understanding of the biology of the disease, or the mechanisms of a drug to appreciate which studies provide strong or weak evidence of meaningful clinical benefit if the key outcome findings are reported completely, consistently, and background information is provided about each of the key elements in a resource linked to the report.

In **Table 1** which follows, we provide our draft proposal:  
a **T**abular format with required outcome **E**lements in **L**ogic **L**ocations (TELL).

In **Table 2**, we propose reader-friendly but concise explanations of TELL elements for the public and the media. Each should be considered starting points or suggestions from an interested third party: patients!

To journal editors who may worry about the space requirements of a TELL-like format and the associated costs, we note that improving the clarity and objectivity of clinical reporting seems an excellent tradeoff. Further, free-form abstracts might still be used by journals and professional organizations if the abstract or full paper includes a link to a TELL – a more complete and structured report. The full text of the published paper could then provide the technical illustrations and in-depth background for scientists, on the biology of the diseases and mechanisms of actions, which would continue to nurture productive conversations and support continuing progress against human disease.

Advantages of Standard Reporting in a TELL-like format:

- Enhance the ability of the scientific community to efficiently filter and weigh reports, and compare results across different studies and journals.

<sup>3</sup> Wood, Alastair J.J. **Progress and Deficiencies in the Registration of Clinical Trials** N Engl J Med 2009 360: 824-830

<sup>4</sup> Daniel M. Cook et al; **Reporting Science and Conflicts of Interest in the Lay Press** PLoS ONE. 2007; 2(12): e1266. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2092382/>

- Help sponsors and clinical investigators to make better decisions when designing clinical studies – to measure TELL events.
- Act as a deterrent against intentional or unintentional sponsor/investigator bias and common media-born misinformation.
- Discourage reporting of clinical data that has not yet matured.
- Help build support and improve public confidence in the objectivity of clinical science, needed to merit public funding of NIH.
- Provide a stronger basis for informed consent among patients and their treating physicians when considering clinical trials based on preliminary evidence of efficacy and safety.
- Foster more objective judgments among financial investors about which candidate drugs have the most potential, helping to attract needed capital to the more deserving inventions, while letting the less promising agents fail faster.
- By providing universal templates for abstracts the authors may produce higher quality abstracts more efficiently.
- And, as noted, such reporting would be complementary to the NIH initiative to expand the Clinical Trials Registry and Results Database. The results could be efficiently ported, from one registry to another if it is first reported in a structured way.

Finally, we have observed in FDA drug advisory committee reviews that the review is usually based on outcome events and detail about the study population (the context), as included in TELL below. Such information is rarely if ever proprietary – in need of protection from public disclosure.

Karl Schwartz  
 President, Patients Against Lymphoma  
 www.lymphomation.org

See TELL Tables 1 and 2 below.

**Table 1**

| Elements   | TELL Report Format (proposed starting point):  |  |
|--|--|--|
| <b>N</b><br><br><b>Evaluated / Intent to Treat</b> | Number of participants in the clinical trials - Evaluated / Intent to Treat.<br><br>We propose that intent to treat be included in all clinical research abstracts, expressed as:<br><br>N = Evaluated / ITT<br>Example: N = 300/500         |  |
| <b>Population</b><br><br>(clinical circumstance)   | Medical condition (subtypes):<br>Risk: High, medium, low risk<br>Performance index   Prognostic index<br>Median age: in study / general population<br>Median number of prior therapies (types if relevant)<br>Genetic characteristics if any | <b>Arm2:</b><br><br>Balanced risk factors? |
| <b>Study Type</b>                                  | Phase of study:<br>Randomized / Single-arm<br>Prospective / subset analysis  |  |
| <b>Study Regimen</b>                               | Drugs and doses:<br>Abbreviated:<br>Full names:  | <b>Arm2:</b>                               |
| <b>Regimen Administration</b>                      | Cycle = x, Number of Cycles,<br>Number of Treatment Days,<br>Treatment Duration in weeks<br>Route: Oral, IV, Continuous infusion...  | <b>Arm2:</b>                               |
| <b>Primary Clinical Questions</b>                  | Median Overall Survival (OS):<br>Quality of Life (QOL):<br>Surrogates for OS/QOL:<br>CR rate, Progression Free Survival ...<br><br>Single-arm: Pre-specified goal relative to historical control:  |  |

|                                     |   |              |
|-------------------------------------|---|--------------|
| <b>Primary Clinical Findings</b>    | Expressed as Rate, include Confidence range:<br>Evaluated: CR/n (%) (CI range)<br>Intent to Treat: CR/n (%) (CI range)<br>Primary endpoint met: Y/N?  | <b>Arm2:</b> |
| <b>Secondary Clinical Questions</b> | Endpoints:<br>Safety   Overall response rate   CR rate,<br>Progression Free Survival,   Survival ...<br><br>Provide pre-specified goal (relative to historical control) if a single-arm study<br>Secondary endpoints met? | <b>Arm2:</b> |
| <b>Secondary Clinical Findings</b>  | As defined in Secondary Clinical Questions<br>Expressed as Rate, include Confidence range, such as:<br><br>Evaluated: CR/n (%) (CI range)<br>Intent to Treat: CR/n (%) (CI range)   | <b>Arm2:</b> |
| <b>How Endpoints were measured</b>  | By: Independent / Investigator / Centralized<br>Schedule (weekly, monthly):<br>Assessment type (blood, imaging):  | <b>Arm2:</b> |
| <b>Maturation of Data</b>           | Completed / Interim?<br>Time to full enrollment / analysis:<br>Median time of follow up:<br>Need for follow-up? Yes/No  |              |
| <b>Safety Results</b>               | Expressed as rate with range:<br>By grade (severity): Serious first.<br>For Evaluated: SE/n (%) (CI range)<br>For ITT – (indicate if toxicities led to dropping out)  | <b>Arm2:</b> |
| <b>Mortality</b>                    | Death rate: Treatment-related: , Other:<br>On study   Off Study<br>Evaluated   Intent to Treat<br>Expected rate in this population:   | <b>Arm2:</b> |
| <b>Limitations</b>                  | Free text area. Authors describe main limitations of the study methods and design – such as sample size, or study type ... to describe level of evidence and if findings are consistent with other studies                |              |
| <b>Discussion</b>                   | Free text area.   |              |

**TABLE 2**

| <b>Elements</b>  | These are proposed explanations of TELL elements, which to save space would not be included in published abstracts but could be available on the Internet for the public and media.  |
|--|--|
| <b>N</b><br><br>Evaluated /<br>Intent to Treat<br><br>A way to judge the power of the study at a glance. | Stands for the number of participants in a study. It provides the denominator - a way to estimate the rate of results in the real world. To illustrate by extreme example, imagine how little confidence we can have in a study of two patients, reporting a 100% response rate.<br><br>A denominator is absent from case reports and testimonials – a reason such reports are described as anecdotal – which is shorthand for not evidence of causality (that the intervention caused the result); nor can such accounts predict outcomes for others – which is the objective of clinical research. |
| <b>Intent to Treat (ITT)</b>   | Study results from a pre-defined N (or prospectively defined patient sample) provide more confidence than a numbered determined by chance, circumstances, or investigator ad hoc decisions. The latter could be determined when the outcome is most favorable, which undermines the integrity of the result.   |
| <b>Population</b><br><br>Clinical Circumstance / Patient Selection                                       | This number accounts for <b>all of the participants</b> that enrolled in the study, not just those who completed the protocol and were available for evaluation. When the ITT is greater than the number Evaluated, it calls into question the integrity of the analysis, and how well it could apply to results in the real world.  |
| <b>Study Type</b>  | How scientists and regulators interpret the results of a study is dependent on the population – the natural history of the disease untreated, or treated differently, but also the characteristics of the participants (age, performance, number and type of prior therapies). Did the study population have low or high-risk disease? For example, response rates in previously untreated lymphoma patients can be more difficult to interpret than in those who have received many prior therapies.  |
|  | Randomized studies provide the most objective basis for identifying and comparing risks and benefits, relative to the control therapy – typically the control is the current standard of care. Dose-finding studies are done to guide the design of subsequent studies, not to establish claims of medical benefit.  |

|  |   |
|--|---|
| <p><b>Clinical Findings</b></p> <p>Does the intervention as measured by the chosen <b>endpoints</b> reasonably predict improved survival or quality of life?</p> | <p>Endpoints describe what is being measured to help to judge if the intervention provided meaningful clinical benefit – net benefit or harm. Of the endpoints used in clinical research, <b>survival</b> is the most reliable as it accounts for known and unknown effects in the near- and long-term.</p> <p>However, survival differences cannot always be measured for conditions that have a long clinical course, especially where other treatments will confound assessment. Surrogate endpoints, such as Progression Free Survival (PFS) may or may not predict clinical benefit – depending on the magnitude of the difference and with consideration of the possible offsetting side effects. Response rates do not reliably predict clinical benefit. Complete Response (CR) rates, however, if strongly associated with durable remissions, can be a useful surrogate for predicting clinical benefit in some settings.</p> <p><b>Safety</b> reporting should be reported as prominently and clearly as efficacy, using rates of events to help patients and physicians to judge the risks at a glance. Clinical benefit is based on the consideration of both efficacy and safety, thus safety endpoints are more important in studies that use surrogate endpoints for efficacy, because survival reflects both effects negative and positive of therapy.</p> |
| <p><b>Regimen Administration</b></p>   | <p>Patients will want to know how the drug is administered: orally, by IV, by continuous infusion, and the duration of treatment – and how that might compare with competing therapies.</p>   |
| <p><b>Methods: Assessment Maturation of outcomes</b></p>   | <p>Notably, Independent data monitoring (often used in pivotal phase III trials) guard against biased interpretations of imaging results, Even after a study has completed the administration phase, many months or years may be needed to measure the endpoints, such as time to progression. (A reason that validated biomarkers that predict longer-term outcomes are urgently needed to accelerate progress.) Safety issue can take many years to emerge and may not be captured at all if the participants are not followed for a long enough time.</p>  |
| <p><b>Limitations</b></p> <p><b>Efficacy and Safety Findings</b></p>   | <p>To reliably calculate the response rates in the study population requires a pre-defined defined denominator (N), which is the basis for estimating the rates for study drug effects in the general population. Notably, case reports and testimonials, lacking a denominator (the number of participants), cannot be used to determine if the intervention even caused the outcome, or how likely the reported outcome will occur in others – which is critical to medical decision making. Was the population large enough to form conclusions about risks and benefits for others? Was the follow-up long enough to judge the result? Is the endpoint a validated surrogate for meaningful clinical benefit? Was there a control group –and randomized selection to protect against patient-selection bias? Are the findings consistent with findings in similar populations in studies carried out by independent groups?</p>   |
| <p><b>Mortality</b></p>  | <p>Treatment-related mortality events can be a challenge to distinguish from other causes. (Another reason that a survival benefit is the most reliable endpoint for comparing the potential of protocols to provide clinical benefit.) Treatment-related mortality can be acceptable in a population with high-risk disease, if these events are less common than mortality resulting from disease progression when treated differently.</p>   |
| <p><b>Discussion</b></p>   | <p>Experts have noted that the conclusions of research authors are prone to bias, statements which can be considered a conclusive finding by the general public when published or quoted by the press.</p>  |