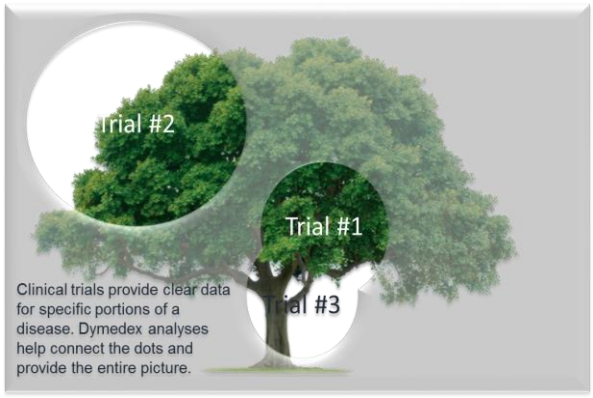
The Big Picture:
Why understanding a disease landscape requires critically evaluating and synthesizing a large body of clinical literature

Summary
Your understanding of the market size for your technology may be deeply misinformed, leading to suboptimal decisions, inappropriate strategies, and misdirected investments –- or worse!

Many companies construct their view of a market from only a handful of clinical papers. Due to the inherent bias that exists within many clinical studies, this approach can lead to a highly skewed viewpoint and a misunderstanding of the true realities that exist within the market.

This white paper discusses important pitfalls that can undermine the validity of the findings of clinical studies.

Creating a view of the market landscape from only a handful of clinical papers or industry reports can lead to a grossly skewed or misinformed view of the market and the macro-level dynamics that influence disease prevalence on a population-wide basis. A single paper provides only a snapshot of an entire landscape and fails to capture the complex interacting and overlapping segments that exist within any disease population.



Clinical trials, even if designed in a manner to avoid bias and sufficiently powered to capture significant associations, often have strict inclusion and exclusion criteria and are composed of groups that have a completely different age distribution, comorbidity burden, diagnostic status, or treatment regimen than exists within the larger disease pool. In addition, disease populations are fluid: as diagnostic and therapeutic landscapes are continually evolving over time, the insights and conclusions from clinical studies become less relevant as time passes. Therefore, a comprehensive understanding of any healthcare market requires synthesis and analysis of a large body of the most up-to-date clinical papers.

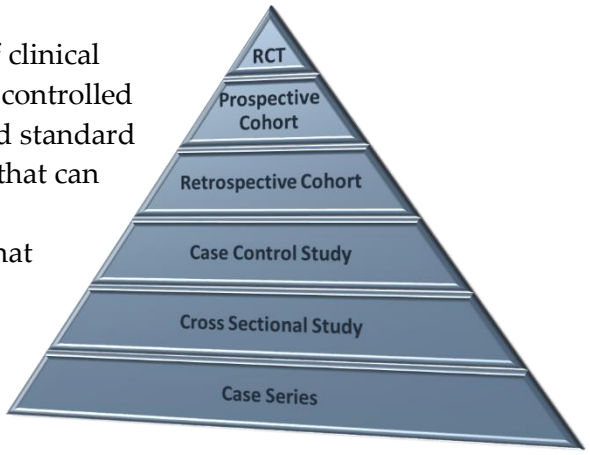
However, synthesizing clinical literature and integrating data from multiple sources into a comprehensive view of a disease population, while necessary, is challenging given the heterogeneous nature of study design, the degree of data reporting, and the methodologies used for analysis and interpretation of data that are found throughout clinical studies. For example, two papers may report entirely different prevalence rates for a disease depending on

the differences in the sizes of the study populations, the year(s) during which data was collected, and the age, gender, and ethnic distributions that comprised the study sample.

Data frequently needs to be normalized in order to make points from two different studies comparable. For example, if two studies were performed during a different time period or in populations with a different age structure, then the observed age-specific rates for each study must be applied to a standard population-based age distribution. This age-adjustment of the data not only makes these two data points comparable, but also adjusts for any crude differences that occurred due to variability in sample populations. Crude rates from two different studies cannot simply be averaged to arrive at an actionable conclusion on the relative sizing of important metrics such as prevalence or incidence for a given disease, instead, they must be carefully analyzed and normalized.

While the analysis and synthesis of clinical literature into a comprehensive view of the market landscape requires a large body of clinical papers, the accuracy of any market analysis is utterly dependent on the validity of the data used. Clinical research is the foundation of evidence-based medicine, informing everything from the therapeutic guidelines for the standard of care to the overall understanding of the epidemiologic disease landscape that exists within the population. However, just because research is published in a well-respected and highly cited journal does not mean that the data is always accurate. An evaluation of 45 highly cited original clinical trials published in three major medical journals during 1990-2003, revealed that 56% were either contradicted, unchallenged, or found stronger effects than subsequent studies[1].

While a well-established hierarchy for evaluating the strength of clinical evidence exists and is based on study design, even randomized, controlled trials that represent the top of the evidence pyramid and the gold standard for evidenced-based guidelines are not exempt from the pitfalls that can skew results and impact the validity of data. Recently, a study evaluating 37 re-analyses of randomized clinical data revealed that 35% of the re-analyses led to different findings and implied conclusions than originally published[2].



Pitfall #1 – Reverse Causality

Reverse causality occurs when a correlation between Cause A and Effect B is then misinterpreted as evidence that Effect B was due to Cause A. The temporal sequence between exposures and outcomes in a clinical study is not always captured due to the study design making the findings between associations prone to reverse causality bias. Retrospective studies are particularly at risk as the study timeline is not adequate enough to confirm that Cause A really does precede Effect B. In addition, prospective studies, while at lower risk, may still be subject to this pitfall if there is a high degree of undiagnosed disease with the baseline study population.

1. Ioannidis. Contradicted and Initially Stronger Effects in Highly Cited Clinical Research. JAMA. 2005;294(2):218-228.
elevation. N Engl J Med 2001;345:494-502
2. Ebrahim *et al*. Reanalyses of randomized clinical trial data. JAMA. 2014:312(10):1024-32.

Pitfall #2 – Random Chance

Random chance can impact the associations between variables X and Y, as there is always the possibility that an association is truly valid or that it exists merely due to chance. The probability that an association is valid is evaluated on the basis of statistical tests. While the use of statistical tests is common in peer-reviewed literature, there is data to suggest that statistical errors including inappropriate use, interpretation, and reporting are common even in the most well-respected journals. An evaluation of 53 papers published in either the New England Journal of Medicine or Nature Medicine during 2004 found that inaccurate or suboptimal statistical tests were observed in 16.1% of articles published in the NEJM papers and 27.1% of the articles published in Nature Medicine[3].

Statistical tests are commonly interpreted using a P-value which is a metric used to quantify the probability that the observed relationship between two variables is due to random chance. Traditionally, a P-value < 0.05 is considered statistically significant, meaning that the probability of observing the same relationship or effect based on pure coincidence is less than five percent. However, P-values need to be analyzed with caution, as they are not as objective or accurate as they are often interpreted to be, and can be challenging to interpret when study samples are small, follow up is short, accrued events are infrequent, or multiple groups or endpoints are being analyzed.

Pitfall #3 – Selection or Information Bias

Bias is a systematic error in study design that results in an association between X and Y in the study population that does not exist in reality among the target population. While many types of bias occur, they can be sub-classified into two main types known as selection bias and information bias. Selection bias occurs when there is non-random selection of study participants. This can occur when patients are lost to follow up, selected from a healthy or volunteer population, or composed entirely from an inpatient population. Information bias is due to measurement error of an exposure or outcome. This type of bias can occur due to any mode of information gathering that distorts it, such as the methodology in which information is collected or interpreted by the observer, the ability of the participants to recall information, or changes in behavior of study subjects due to awareness of study participation.

Both selection and information bias represent key pitfalls that can distort information and skew the interpretation of clinical findings. Selection bias is less likely when a study population is randomized in order to decrease the risk of creating an isolated concentration of any characteristics or variables in the study groups, as well as ensure that the study groups are an appropriate comparison. The risk of information bias is greatly mitigated in studies that incorporate blinding into their study that reduces the influence that experimental procedures and interpretation of outcomes may have on study subjects and observers.

Pitfall #4 – Confounding

Confounding occurs when there is an association between two factors that is influenced by a third factor that does not lie within the causal pathway, but is independently associated with both the exposure and the outcome. As a result, a confounding factor distorts the magnitude of the association between the exposure and the outcome.

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3. Strasak *et al* The Use of Statistics in Medical Research: A Comparison of "The New England Journal of Medicine" and "Nature Medicine". The American Statistician 2007: 61(1): 47-55

All observation studies are prone to confounding bias. While there are ways to design a study and analysis to mitigate the risks of confounding, some degree of confounding will occur. Strategies to mitigate the risk of confounding include running a stratified analysis where the association between exposure and outcome are assessed at different levels, crossover studies in which subjects act as their own controls, and randomization that equally distributes both known and unknown confounding variables between the two treatment groups.

Pitfall #5 – Exaggerated Risk

Even if a trial was run correctly and risks of bias were appropriately mitigated by the study design, selection of the statistical tests for analyzing data still need to be applied appropriately and presented in a way that they will be accurately interpreted by readers. Exaggerated risk can occur if a study does not appropriately define the statistical metric used to characterize the relationship between two variables. This commonly occurs in the medical literature when relative risk is used instead of absolute risk.

A notable example of exaggerated risk occurred when the CURE study – a randomized controlled trial evaluating the combination of clopidogrel and aspirin vs aspirin alone in patients with acute coronary syndromes[4] –was published in 2001. Many cited the statistic that clopidogrel plus aspirin reduced the risk of heart attack, stroke and cardiovascular death by 20 percent. However, citing this statistic is misleading, as this figure referred to the relative risk reduction. The absolute risk reduction of this drug combination was only 2.1 percent. Consequently, the statistical metric reported by any study can have significant implications for the interpretation of clinical data and, if not carefully selected and understood, can often lead to misinterpretation.

Critical evaluation of the clinical literature is crucial to accurate market analysis

A market landscape is rarely homogenous, but often contains subsegments that are more attractive than others based on accessibility and compellingness. However, companies frequently fail to accurately size and characterize the various segments that exist within the indicated opportunity, and the ones that do, often incorporate biased and inaccurately interpreted clinical literature in the foundation of their analysis. When developing and prioritizing strategic investments to drive market adoption, a rough estimate of market size and a high level view of the market segment isn't enough.

Dymedex applies an objective, scientific, and data driven approach to market analysis. Rather than overvaluing one article, we synthesize all available viewpoints in the clinical literature, critically reviewing key references with an eye for the major pitfalls that can invalidate clinical data. We dig deep to assemble a comprehensive evidence base to validate or invalidate our hypotheses and to understand the realities of the market at the most granular level. The end result is an integration of hundreds of peer-reviewed papers, industry data, and key insights that form a comprehensive understanding of the true market opportunity that is actionable and can inform key business strategies. At Dymedex we believe *knowing is everything*.

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4. Yusuf S et al. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without STsegment
elevation. N Engl J Med 2001;345:494-502