Our Love/Hate Relationship with Clinical Surveillance, and Why Both are Valid.

As clinical researchers, we are continuously reminded of the threat and expense of trial failure in late stage development\(^1,2\). In CNS diseases, where surrogate biomarkers are largely absent, drug effects are modest, and nearly all FDA/EMA-sanctioned outcome measures are subjective and highly vulnerable to error, these threats are particularly real. While we anxiously await a promising future of validated biomarkers that will increase diagnostic and measurement precision, our patients’ medical need continues to grow. Clinical trialists must now focus on methods to meaningfully enhance the existing research paradigms. Innovative study designs that address runaway placebo response rates are an excellent first step\(^3,4\). Medication adherence-monitoring technologies that assess whether our trial participants are actually participating in our trials are not far behind\(^5\). And then there is clinical surveillance. Despite the negative connotations suggested by its name, clinical surveillance can be implemented as a fully transparent, extremely collaborative, and highly creative next step in shoring up traditional research paradigms.

CNS researchers have implemented surveillance strategies from within pharmaceutical companies, through contract research organisations (CROs), or by using one of the many innovations offered by surveillance vendors in our field. The universal goal of all surveillance systems is to increase the chance of trial success by improving patient and data quality. Surveillance strategies aim to ensure that patients entered into our trials are fully qualified, that efficacy assessments are administered and scored reliably, and that unwanted heterogeneity is controlled, all of which necessarily result in preservation of statistical power\(^6,7\). Throughout industry, we find experienced clinical scientists applying years of academic research and clinical training to create innovative data oversight solutions, including expert review of recorded audio- or videotaped interviews, tandem patient and clinician ratings, evaluation of rating scale data to identify probable rater error, and web-based clinical interviews by calibrated centralised raters.

So does surveillance make a difference? The resounding answer is “yes.” Our own immediate measures of success are that we identify hundreds of inappropriate subjects before they are randomised and can negatively impact trial data, and we detect scale administration and completion problems that are immediately rectified with remediation before the next assessment is performed. We see sites sail through regulatory audits because protocol violations are minimised, and perhaps most importantly, we see positive effects on placebo response rates compared to historically similar trials. Until that day when industry is able to fund fully powered, prospective, randomised trials to assess the benefit of surveillance vs. no surveillance on signal detection, these quality indicators are the strongest arguments we have in favour of clinical surveillance. They show irrefutable evidence that surveillance makes a difference, with real results that sponsors and investigators alike can celebrate.

Still, commitment to quality has its limitations, the most obvious of which is site burden. Clinical surveillance is always associated with some increased work for sites. However, the range of burden can span from taking a little extra time to correspond with surveillance clinicians to manoeuvring patients through multiple video interviews for outside review. We believe that the fundamental causes of patient selection and rater error are site workload and protocol complexity\(^8\), such that a guiding principle behind all surveillance should be to enhance and support site activity, not to exacerbate the workload challenge. Our experience is that surveillance is largely accepted, even embraced, when it can be deployed in a manner that respects the valuable time of site personnel, when the methods can be easily incorporated into daily clinic
flow, when sites are compensated for their time, and when surveillance providers and sponsors are willing to adapt based on site feedback. Importantly, we find that those surveillance strategies that are reflective of clinical practice, such as consultations with other clinicians regarding individual cases, are the strategies most acceptable to investigators. The balance between surveillance-supported quality and minimal site burden is not an easy one to achieve, to be certain. We must continuously refine our processes to ensure we are maximising the yield on our own interventions, but deliver in a way that most sites find supportive. Knowing the low probability of success for new compounds, understanding the need to enhance our existing research paradigms, and realising that some departure from tradition is necessary to keep the field moving, we are highly enthusiastic about this next step. When thoughtfully executed, the surveillance interventions available in CNS have the potential to propel us far forward in terms of data quality and trial interpretability, which is progress surely everyone can support.

References


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