

UNBLINDED MONITORING IN HCV TRIALS

Making a Case for a New Standard

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INTRODUCTION

One of the goals of a well-designed clinical study is to minimize conscious or unconscious bias by keeping principle participants (i.e., investigator, subject, and sponsor) blinded to the investigative treatment assignments. Such double-blind trials allow more robust analyses of study data and greater confidence in final interpretations—but what if the blinded study design stands in the way of standard treatment modification decisions, or compromises the safety of the subject by not permitting monitoring of key disease markers on a real-time basis?

HCV TRIALS AND THEIR CHALLENGES

Hepatitis C Virus (HCV) infects nearly 200 million people worldwide with an estimated 35,000 new cases being diagnosed in the United States alone each year.¹ About 80 percent of all HCV infections become chronic and many progress to chronic liver disease. In a recent study, HCV infection was associated with a 77-fold increase in the risk of

primary liver cancers when compared to the general population.² Current standard of care (SOC) treatment for chronic HCV infection includes a 24- to 48-week course of pegylated interferon and ribavirin, depending upon the genotype of the virus. Even so, a sustained virologic response (SVR) is achieved in only 45 percent of those with genotype 1 HCV.³ Given the significant side effects associated with SOC treatment, there is a clear unfilled need for novel anti-HCV therapeutic agents—a fact reflected in the more than 350 HCV active clinical trials in the United States.⁴

The goal of current HCV clinical research is to identify new antiviral agents specifically targeting hepatitis C (STAT-C therapies) and to determine how best to individualize treatment regimens in order to optimize outcomes (i.e., increase the SVR rate) and minimize both drug toxicity and the development of resistance. Further consideration must be given to the very heterogeneous nature of the HCV population. Variables such as viral genotype, IL28B polymorphism, baseline viral load, degree of liver damage, and prior history of HCV treatment can result in differing viral response rates.

The challenge to individualizing treatment strategies is to keep all of these variables in mind while carefully monitoring individual treatment response so that, ultimately, shorter durations and lower dose regimens are utilized for rapid responders while reserving longer durations and higher dose regimens for those patients responding more slowly.

Additionally, treatment needs to be discontinued early in situations where patients are deemed to be nonresponsive to therapy in order to minimize development of viral resistance to failed treatment.

DOUBLE-BLINDED PROTOCOLS: AN ADDITIONAL HURDLE

In research, one of the major hurdles is being able to provide these individualized treatment and safety considerations within the constraints of a double-blinded clinical trial protocol. For HCV infection, the clinical standard for judging treatment response involves observation of plasma HCV ribonucleic acid (RNA) titers and temporally comparing them to pre-treatment baseline values. Unfortunately, the kinetics of declining viral titers can be characteristic of different treatments, making maintenance of the blind among experienced investigators difficult should they be allowed to monitor individual subject HCV RNA profiles. Nevertheless, these HCV RNA results need to be monitored in order to make decisions regarding whether investigational therapy should be continued, stopped for treatment success, or stopped for treatment failure. As a solution, i3 has developed a novel “unblinded monitoring” service to provide sufficient real-time information to investigators so that they can most appropriately manage their patient’s therapy while remaining blinded to the patient’s actual HCV RNA levels and antiviral treatment assignment.

THE CASE FOR UNBLINDED MONITORING

Unblinded HCV RNA monitoring was designed by InVentiv Health Clinical as an integral component of the HCV clinical trial team.

The InVentiv Health Clinical unblinded team is typically composed of a core cross-functional group of experienced data processors, statisticians, and medical monitors. On a regular basis, the InVentiv Health Clinical team receives lab data transfers, creates quality-controlled and validated data lists, and reviews the virologic status of each subject within the context of his/her treatment stage. The listing programmatically flags instances where viral titer thresholds are breached and reflects situations where treatment modifications may be necessary. A set of treatment modification rules is pre-defined in the protocol and based on accepted HCV response definitions, including virologic breakthrough, early virologic response, sustained virologic response, and virologic failure. Such virologic response definitions are often accepted as surrogate markers of clinical response by regulatory agencies. When treatment modifications become warranted, following review of viral load data, the

InVentiv Health Clinical unblinded medical monitor immediately communicates subject-specific treatment options to the investigative site without revealing critical treatment group assignments. Site personnel are required to verify receipt of all treatment modification directives. Should a given subject's response to treatment progress in a safe and appropriate manner, InVentiv Health Clinical communicates this in the form of regular periodic site communications.

In addition, InVentiv Health Clinical's ongoing unblinded monitoring has provided the additional service of identifying specimens that meet specific criteria for viral sequencing during the conduct of the study, as well as identifying ambiguous or irregular data in real time and requesting the collection of additional specimens when appropriate. Performance of these activities concurrently with study conduct rather than waiting until after database lock contributes to overall improved study timelines. Furthermore, interval monitoring of pharmacokinetic parameters within specific populations of patients on concomitant treatments has been performed in order to identify potential drug interactions between investigational therapies and critical treatments for other coexistent conditions, the results of which are communicated to an independent safety monitoring committee.

CONCLUSION

In summary, the most desirable HCV trial designs allow subjects, investigators, and operational project team members to remain blinded to treatment assignments and subject HCV RNA data, while still being able to provide optimal treatment recommendations based on current SOC and a means for

ensuring subject safety. To accomplish this, InVentiv Health Clinical has assembled an experienced, cross-functional, unblinded monitoring team which has performed these services for several HCV clinical trials. InVentiv Health Clinical's unblinded services can also be combined with traditional blinded operational and medical services, where the unblinded team communicates with the blinded team appropriately to maximize efficiencies while keeping essential and auditable records verifying maintenance of the blind. With extensive experience performing HCV clinical trials, an unsurpassed breadth of service offerings, proven processes and procedures, and a strong commitment to the overall integrity of these studies, InVentiv Health Clinical stands uniquely qualified to manage all aspects of HCV clinical trials.

REFERENCES

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