The Evolving Role Of Healthy Participants In Early Immuno-Oncology Trials

Studies in healthy participants have long been a cornerstone of early clinical development. In most therapeutic areas, first-in-human (FIH) trials are conducted in individuals without the target disease because they offer an ethically and scientifically efficient way to understand a new drug's pharmacokinetics, tolerability, and early pharmacodynamics before exposing vulnerable patient populations. Healthy participants are easier to recruit, adhere closely to protocol procedures, and provide data uncontaminated by comorbidities or concomitant medications. For these reasons, such trials traditionally serve as the foundation upon which later patient studies are built.

For much of modern drug development, the idea of conducting oncology studies in healthy participants would have been inconceivable. Early cancer therapeutics were broad cytotoxic agents that exerted their effects by indiscriminately damaging rapidly dividing cells. These mechanisms, by design, carry risks that are ethically unacceptable for individuals without disease. As a result, oncology studies are mostly restricted to patients with advanced cancers who lacked therapeutic alternatives. The primary aim of these trials was (and still often is) to establish the maximum tolerated dose rather than to interrogate mechanism or optimize pharmacology. In other words, safety, and not pharmacology, guided dose selection.

This paradigm has shifted dramatically with the rise of targeted therapies and immuno-oncology (IO) agents. Modern immunotherapies no longer depend on blanket cytotoxicity but act by selectively modulating immune pathways that are functional in both healthy and diseased individuals. Checkpoint pathways, cytokine receptors, chemokine axes, intracellular kinases, and metabolic immune checkpoints can all be studied in physiologically intact immune systems. Many of these mechanisms are reversible, quantifiable, and supported by nonclinical data that predict an acceptable safety profile, which makes early explorative studies in healthy participants advantageous. Thus, although once viewed as an exception, the integration of healthy participants into early immuno-oncology programs is becoming an important and rational development strategy.

The reason lies in how much immuno-oncology has evolved. Contemporary immunotherapies act on pathways that are present and measurable in healthy physiology, allowing drug developers to assess pharmacokinetics, target engagement, and early pharmacodynamics with far greater clarity than in oncology patients. The immune system in late-stage cancer is often profoundly altered by disease, prior therapy, or chronic inflammation. Baseline variability is high, cytokine responses may be blunted, and T cells can display exhaustion or dysfunction. These confounding factors can mask subtle pharmacological signals and complicate interpretation. In contrast, healthy participants offer baseline stability, predictable physiology, and far cleaner pharmacodynamic readouts.

Of course, not all immunotherapies are suitable for this approach, and careful selection remains essential. However, a clear framework has emerged. First, a compound's mechanism must be active and measurable in the absence of cancer. Targets such as adenosine receptors, CXCR4, SYK, MEK, or elements of innate immune sensing are expressed in peripheral blood or accessible tissues and can be interrogated directly. Second, robust pharmacodynamic endpoints must exist, whether proximal markers of target engagement, cellular activation markers, cytokine modulation, or system-level effects observed in controlled human challenge models. A study in healthy participants offers real value only when it contributes mechanistic insight. Third, the investigational therapy must have an acceptable safety profile for healthy participants, supported by nonclinical toxicology, dose projections, and the reversibility of effects. While broad checkpoint inhibitors are still unsuitable for full-dose HV studies, more selective next-generation immunotherapies may be explored safely at low doses or for short exposures.

When these conditions are met, the scientific advantages become compelling. Pharmacodynamic responses are easier to detect and interpret in the clean environment of healthy physiology. Recruitment tends to be faster and more predictable, and retention is markedly higher. Healthy participants, unconstrained by disease burden or treatment fatigue, adhere more closely to protocol procedures and complete intensive sampling schedules that would be impractical in oncology patients. This operational efficiency translates directly into higher data quality and significantly more informative PK/PD modeling. It also simplifies dose selection. For example, for immunotherapies, escalating to the maximum tolerated dose is neither necessary nor desirable. Excessive immune stimulation may trigger exhaustion, paradoxical suppression, or severe immune-related adverse events. Instead, the goal is to identify the pharmacologically active dose - the exposure at which biomarkers confirm target engagement and balanced immune activation. That is why early-phase studies in healthy participants are ideally positioned to define this window well before the first patient is recruited.

One of the most powerful tools in this setting is the use of controlled human immune challenge models, which allow system-level responses to be measured in real time. Lipopolysaccharide (LPS) induces a short, well-characterized inflammatory response that induces innate immune pathways relevant to many IO agents. Keyhole limpet hemocyanin (KLH) provides a controlled activation of adaptive immunity, triggering both T-cell and antibody responses that can be sampled in blood and skin. UVB irradiation or topical imiquimod stimulates local tissue inflammation and enables repeated biopsy-based analyses, which offers a unique view into tissue-level immunopharmacology. These challenge models create standardized, reproducible immune perturbations against which the effects of investigational compounds can be observed and quantified.

The growing relevance of healthy participants in immuno-oncology is strongly supported by empirical evidence. In a systematic review conducted at the Centre for Human Drug Research (CHDR), 38 different immunomodulatory compounds have been investigated in healthy participants, as of October 2020 (Radanovic et al, 2022). Some studies included detailed pharmacodynamic assessments ranging from flow cytometry and cytokine profiling to epigenetic markers of immune cell stability and, in several cases, readouts from LPS or other challenge models. Many of the immune pathways investigated - such as cytokine signaling, innate immune activation, or metabolic immune checkpoints - are directly relevant to oncology, which confirms the feasibility of such approaches for IO programs.

The operational advantages observed can be significant. Such trials are expected to be completed faster, with shorter recruitment windows, fewer protocol deviations, and significantly lower dropout rates. More intensive sampling schedules, essential for high-resolution PK/PD modeling, are also possible. Those studies can thus inform dose selection for subsequent patient cohorts, which reduces uncertainty and improving the efficiency of later phase trials.

A recurring challenge in early immunotherapy development is unintended immune activation. Adverse immunostimulation (AIS) can manifest as cytokine release, complement activation, or IgE-mediated reactions. Studies in healthy participant studies, when equipped with standardized sampling windows and mechanistic biomarker panels, provide a controlled and well-monitored setting to detect and characterize such events. Measuring tryptase, IL-6, TNF, IFN-γ, or complement activation products at baseline, at symptom onset, and during resolution enables investigators to distinguish among mechanistic pathways and to adjust dosing or infusion strategies accordingly.

Such studies also offer a practical bridge between preclinical and clinical development when paired with high-dimensional technologies such as flow cytometry, transcriptomics, and tissue-level analyses. For example, RNA sequencing after LPS-induced immune response in healthy participants can reveal oncology-relevant transcriptional signatures, including the upregulation of pathways such as PI3K signaling or MYC in bone marrow during acute inflammation. Such findings demonstrate that short, controlled inflammatory stimuli can be used to induce and characterize pathways that are dysregulated in cancer. They provide a mechanistic toolbox for testing whether investigational IO agents modulate these targets in vivo as expected from nonclinical studies.

To summarize, by enabling precise target engagement studies, clean PK/PD modeling, real-time biomarker assessment, and controlled challenge interrogations, studies in healthy participants reduce the risk of late-stage failures in drug development, accelerate decision-making, and improve both scientific and operational outcomes. Practically, they are easier, faster, and less expensive to conduct, with significantly lower dropout rates and better compliance, leading directly to higher-quality data and greater confidence in early development decisions.

The evolving role of healthy volunteers does not replace the need for carefully designed patient studies. But with foundational mechanistic work completed in healthy participants, patient trials can begin at doses already known to engage the target, with clearer expectations of immune effects and tighter safety monitoring. Such an approach is better aligned with the biology of immunotherapies and targeted cancer agents and represents a meaningful step toward more rational, efficient, and patient-focused oncology drug development. In the era of modern oncology, the inclusion of healthy participants in early-phase trials is no longer an outlier, but it is becoming a scientifically grounded and strategically valuable component of clinical development.