A GUIDE ON

SUCCESSFULLY MANAGING AN AME CLINICAL TRIAL

WORLDWIDE.COM

Have you identified a partner with a proven track record of successfully managing an AME clinical trial?

Despite the large existing market for AME studies, why is it that so few CROs in the United States are able to perform them? It can be hard to find an AME partner because for CROs, the necessary setup is time consuming, labor intensive, and expensive.

To conduct AME studies, a CRO must have a radiation safety officer (RSO) experienced in clinical research trial activities and processes. It must also secure and maintain the appropriate license to handle radioactive materials. This licensure generally involves one or more federal, state, and local governmental agencies. CROs are required to have the proper standard operating procedures (SOPs) and training procedures in place, and these are reviewed by the relevant authorities for approval in specific radioisotopes, such as carbon-14 and/or tritium.

Many clinical pharmacology units (CPUs) — and their associated laboratories — either don't have the space to devote to a separate radioactive area (dedicated space for dose preparation, dose administration, subject confinement, and sample collection) or prefer not to undertake the rigorous training necessary for handling radioactive materials safely. Finding a partner to perform your AME studies in a reasonable time frame, let alone one with an excellent track record, may be a challenge.

At Worldwide, our team can assist throughout your AME clinical trial, from protocol writing through final study report.

Worldwide's experience with and capabilities for performing AME studies

For more than 20 years, Worldwide's Early Phase team has been conducting AME studies, working with up to 150 uCi of carbon-14/IP dose to assist in the determination of drug absorption, metabolism, and excretion of parent compound and metabolites.

Over the past three years, our dedicated, controlled-access CPU in San Antonio, Texas, has conducted on average four mass balance studies per year. (Studies may not overlap to avoid radioactive contamination.) Routine matrices for radioactive recovery include blood, urine, and fecal matter, collected over extended time periods (five days or longer). Procedures have occasionally also included collection of expired air for $^{14}CO_2$. Without exception, these studies have achieved excellent recovery rates (Figure 1) despite some challenging compounds that demonstrated unexpected pharmacokinetic characteristics.

Radioactive materials licenses are held at both our CPU and our bioanalytical laboratory in nearby Austin, Texas. All necessary SOPs and training documents are in place at both locations. In addition, the Worldwide team has a good working relationship with our central institutional review board (IRB).

Worldwide's CPU goes to great lengths to properly handle AME study samples. This includes specific procedures for collection, processing, labeling, and shipping. We work with well-established ground couriers that are licensed for transport of radioactive materials. Sample shipments are made daily to our local laboratory, where they are analyzed immediately. This allows Worldwide to carefully track radiation levels and make informed decisions around radioactive recovery and participant release from our studies.

Some of the lessons and best practices we've learned and developed over the years are:

1. Managing study participants in AME studies requires unflinching attention to detail

Both participant comfort and compliance as well as data quality are top priorities. We make every effort using traditional and novel approaches to recruit and retain the right participants for our studies. AME studies are more challenging in this regard and special considerations apply.

From screening with a careful assessment of medical history and daily bowel habits through informed consent and the instructional and dosing phases, our staff ensures patients fully understand and feel comfortable with the intimate details and importance of total radioactive recovery during these studies.

Subjects must be flexible with their time and provide us with the samples we need. Proactive management of subject expectations includes information regarding:

- No definitive stopping date
- Dry restrooms
- Dietary requirements: high-fiber diet for bowel motility
- 24/7 collection of all urine, fecal matter, and blood sample collection

2. To achieve an excellent total radioactive dose recovery rate, details matter

As shown in Figure 1, the Worldwide team has an outstanding track record of 98.9% radioactivity collection. To attain this level of radioactivity recovery requires careful attention to both dosing and sample collection.

Dosing

It is vital the entire dose is taken. For liquid dose, not one drop can be missed. Liquids are given in wide-mouth containers for easy and efficient delivery. Bottles are rinsed with water and subjects consume the rinse as well, then follow with more water. Finally, the bottles are checked for residual radioactivity.

A Worldwide pharmacist with radiolabel product preparation and administration oversees all dosing and is also available to deliver pre- and post-dose instructions and answer questions.

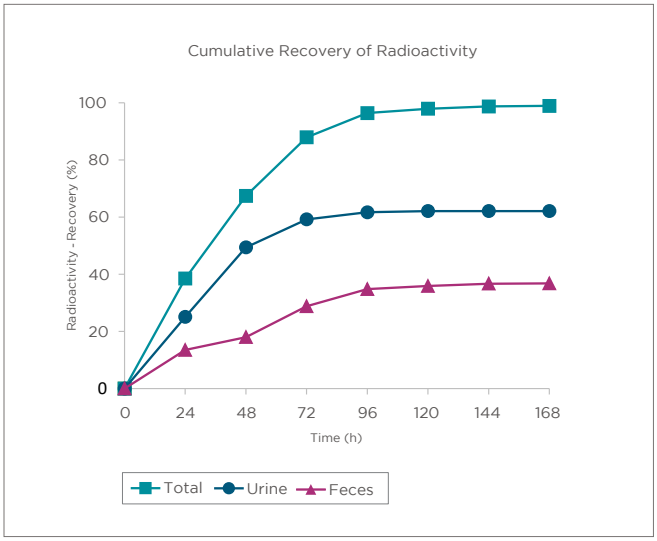

Figure 1. Total radioactivity recovered in sponsor radiolabeled AME studies at Worldwide — 98.9%.

Biological Sample Collection

Reminders are strategically placed around the CPU radiolabel confinement area, especially near the shower, to reinforce the need for collection of all urine and fecal samples. Diet is modified if needed to promote bowel movements. Collection time is typically five – seven days and subjects cannot miss a collection. Once collections are made each day, they are sent to the lab for measurement of radioactive recovery.

3. It's important to build a specialized team for radiolabeled drug research

Safe conduct of radiolabeled studies requires a team of highly trained specialists. Ours includes:

- Radiation safety officer (RSO): The RSO engages in staff training, reviews SOPs, oversees contamination and sample collection testing, and reviews dose calculation, preparation, and administration by the pharmacy.
- Radiologist/sub-investigator: A board-certified radiologist is available in addition to the primary physician investigator for protocol review, comments, for consultation on study design, and to sign off on dose/dosimetry calculations.
- Pharmacists: Full-time, specially trained pharmacists handle and prepare the radiolabeled materials. A CPU pharmacist oversees all the dosing.
- Health physicist: A health physicist consultant reviews the data from preclinical studies and assists in preparation of dosimetry and radiation exposure reports as needed.

Just-in-time, medic and technical staff training is performed to ensure facility staff is up-to-date on their understanding of SOPs, processes and protocol-specific requirements. The RSO covers both the lab and the CPU and is involved in training at both facilities.

4. The onsite cGMP Phase 1 pharmacy must have radiolabel drug preparation experience

A CPU used for AME studies must be licensed and experienced in handling radioactive investigational drugs. The Worldwide CPU's radiolabel pharmacy is capable of hot and cold compounding to achieve target investigational product (IP) dose and radioactivity.

On-site scintillation counting is used to test investigational drug preparations to see that they conform with the target radioactivity. It is also used to confirm full dose administration.

5. Co-location of CPU and bioanalytical lab means convenience and fast results

The Worldwide bioanalytical lab in Austin, Texas, is approximately an hour's drive from our CPU in San Antonio. This proximity enables easy coordination for simplified, daily ground transport and prompt radioanalysis of AME samples. Rapid turnaround with accelerated decision-making is key, as it allows for timely dismissal of individual subjects who have met study objectives.

Our full-service CPU contains 180 beds with flexible procedure space, a cGMP Phase 1 compounding pharmacy, and a CLIA safety lab. At the bioanalytical lab, in-house bioanalytical scientists engage in LC-MS method development and bioanalysis. A comprehensive analysis and final study report of radioactive recovery and PK analysis is performed by the Worldwide Pharmacokinetics Team.

Both lab and clinic must have radiolabel licenses to handle radioactive materials, whether drug product or biological samples. The State of Texas defers to federal regulations for licensing; there are no additional state rules with which to comply. Scintillation counting can be conducted daily to provide timely monitoring of cumulative radioactive output.

6. Sponsors value bioanalytical scientists that can customize services to suit their needs

Worldwide offers true partnership for early phase development, with professionals dedicated to fulfilling the needs of sponsors' unique development programs. Our bioanalytical laboratory sets the bar for efficiency and service and will ensure sponsors receive the AME insights and evaluations they need to make the best possible decisions.

Our bioanalytical lab is flexible in productivity and can accommodate analysis based on your study's requirements. State-of-the-art instrumentation and more than 2,400 validated assays make Worldwide industry leaders in bioanalytical method development and validation.

Collect AME data early to guide development — and satisfy FDA

All NCEs require an AME study. Whether FDA is calling for AME data early or not, plan for AME studies proactively. Since only a limited number of CROs can perform them in the United States, reserve ahead. AME data can add valuable insight at the start of a clinical trial journey and can help anticipate later trial expectations, helping sponsors to save time and cost.

Worldwide Clinical Trials is the ideal partner for AME research. We have significant success and experience conducting AME clinical trials. Sponsors benefit from a highly qualified project team of AME experts. Our integrated lab and clinic facilitate prompt analysis of radioactive samples allowing for efficient subject dismissal.

DON'T WAIT UNTIL YOU RECEIVE A LETTER FROM FDA REQUESTING AME DATA. ACT EARLY TO ACCELERATE YOUR APPROVAL JOURNEY.

ABOUT WORLDWIDE CLINICAL TRIALS

Worldwide Clinical Trials is a global, midsize contract research organization (CRO) that provides top-performing bioanalytical and Phase I-IV clinical development services to the biotechnology and pharmaceutical industries.

Founded in 1986 by physicians committed to advancing medical science, our full-service clinical experience ranges from early phase and bioanalytical sciences through late phase studies, post approval, and real-world evidence. Major therapeutic areas of focus include cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Operating in 60+ countries with offices in North and South America, Russia, Eastern and Western Europe, and Asia, Worldwide is powered by more than 3,000 employee experts.

For more information, please visit **www.worldwide.com** or connect with us on **Twitter**, **LinkedIn**, **Facebook**, and **Instagram**.