Clinical Research Assistants for Intelligent Design and anaLysis (CRAIDL)

Project description

Clinical trials, and especially randomized clinical trials (RCT), are the backbone for clinical decision-making across all health disciplines. However, trials are complex and engage health systems, people and an array of operational, regulatory, institutional and investigative teams. As trials have evolved, the ability to design, deliver and disseminate trial results has increased in complexity and cost while challenging the capacity to deliver timely scientific results to Canadians (and globally). Much of RCTs conception through knowledge mobilization remains manual, subjective, and is inefficient both in the design and the delivery of the trial. Patients cannot easily access or participate in RCTs, and trialists cannot efficiently use the resources available. Science and human health cannot continue to progress this way. Clinical trials in Canada contribute $15 billion annually and the majority are industry rather than investigator driven (available at imc.ca).[1] Many investigators design and develop RCTs, but follow a similar traditional pathway and have utilized processes designed for RCTs of a bygone era - it is now time for creative disruption.

AI tools are being developed across several aspects of RCTs, including patient identification,[2] trial design, designing code for statistical analysis, and event adjudication.[3] However, these elements are just scratching the surface of the potential for, and fulfillment of RCTs with AI. Scientific discoveries are rendered ineffective if not tested in humans and subjected to the highest bar, that of well-designed RCTs that engage and enroll people from the community.

In order to take advantage of recent developments in AI, we propose Clinical Research Assistants for Intelligent Design and anaLysis (CRAIDL), which builds off the RCT expertise at UAlberta, the federal Accelerating Clinical Trials grant (www.act-aec.ca), the AI expertise at UAlberta and other elements available locally and internationally. We aim to build the global center for RCTs leveraging the next generation of tools available to enhance scientific discovery. This grant will create, amalgamate and deploy RCTs of the highest quality and greatest efficiency established in a trusted environment.

Our proposal will use AI-augmentation at every stage of the RCT to remove barriers - from inception of the idea/clinical question, through to knowledge mobilization to the community. Some of the tools needed will be developed by collaborating with the Alberta Machine Intelligence Institute (Amii; amii.ca) Amii colleagues and CIFAR chairs, and others may need to be integrated through global academic and industrial partners. At the major pharmaceutical and device companies, as well as academic research organizations, AI tools have not been deployed fully and often only in a fraction of the parts of a RCT. Our goal is to have every element of a trial utilize AI-augmentation via Agentic design; an AI-first approach. In the AI-first approach, several different AI-focused methods can be used in addition to agentic approaches.

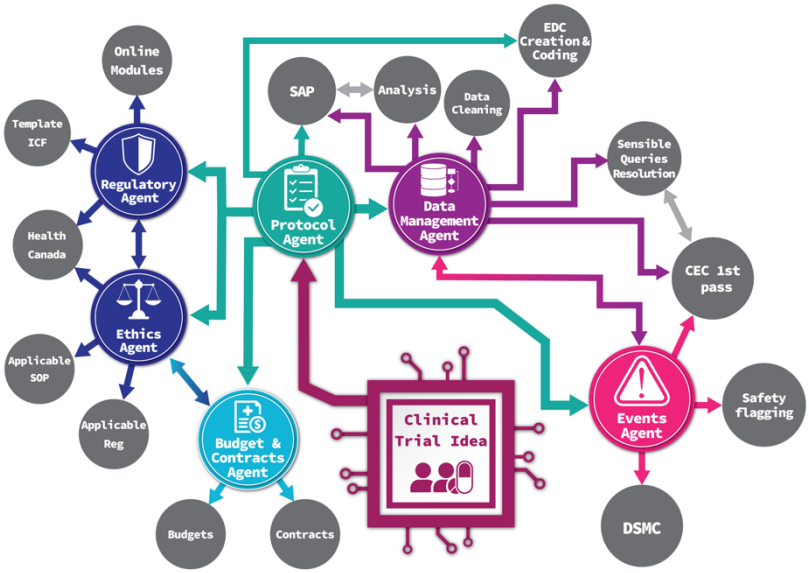
Why agentic design? Agents can function autonomously to a goal-directed behavior, and integrated into and beside other tools. Since agents can be coordinated to act together or independently, adapted to design, and can be part of a human-agent collaboration, this sets up an ideal way to rapidly advance an idea. The adaptable nature allows for integration of internal or external information (e.g. new RCT designs, results of prior trials, updated regulations).

How would this be used? For example, an idea proposed by a clinical researcher based on population health or discovery science work could utilize CRAIDL to advance the idea into a trial to test this further. The faculty member could work with an AI agent which draws from a database of approved RCTs and methodology literature to help develop a customized trial design, from statistical methods to optimal outcomes, patient selection and specialty services needed. Similarly, a clinician, external academic or industrial partner or biotech developer could work through this process as it will remain agnostic to the disease area or health state. From there, this would further develop, optimize, and automate via AI-

augmentation, electronic data capture, monitoring, legal and contractual, and fulfil regulatory requirements. Regulatory, ethical and institutional factors will all be completed via AI-augmentation, as will patient identification within the health system and community. Components such as safety monitoring (including DSMC), event adjudication, analysis, including data science and regulatory submission. Finally, AI-augmentation of knowledge mobilization, such as tools that can be used in a variety of communities for the implementation of the results. Throughout the process, the principles of trust and transparency, and the objectives of achieving efficiency and effectiveness, will be the core of each step.

Work Packages: We will divide the work into 6 core Agents and additional sub-agents.(**Figure**)

Work package 1: The Protocol Agent: this work will help take a question or hypothesis, stated in the typical objective or hypothesis method and with conversational agency will clarify both the question, patient populations, intervention, or control, and initial thoughts on outcomes. From there through conversation with the agent, options for design will be presented. From that refined work, the agent will then further develop your protocol based on the templates that have been used for learning. We will use templates from RCTs that have been completed or are underway and both those that are investigator initiated, and those that are industry supported and publicly available. These will optimize many of the sections required from scientific, regulatory, safety, and other areas.



Work Package 2: The Data Management Agent: this agent will be in charge of integrating with the above protocol agent in terms of statistical design, including developing a statistical analytical plan, preparing mock tables and/or figures with appropriate coding for analysis, as well as existing in the design of creation of the electronic data capture method (e.g. REDCap). This will have sub agents that will be developed for data cleaning and sensible query resolution of data.

Work Package 3: The Events Agent: This agent will work with the above data management agent in order to design the capture of data around the events of the protocol, e.g. primary secondary or tertiary events, and work with the data management agent and the protocol agent in order to ensure definitions and data capture or complete as well as codified in the correct manner to allow for statistical analysis. A subagent focused on clinical events, adjudication, and coordination, will design and operationalize the codified events in order for either human or AI adjudication to occur. A second sub agent will be focused on safety and design the specific adverse or serious adverse event reporting mechanisms required by regulatory bodies. This sub-agent will also be in charge of reviewing the appropriate regulatory structures such as that of Health Canada, or others where there are notification requirements and thus create a system of identification, codification, and submission where appropriate. A third sub agent will be focused on the data safety and monitoring committee work, who are normally responsible for the unblinded safety (and efficacy). This agent will work with the above data management agent and the events agent and other sub agents in order to develop the charter, a statistical analytical plan and methods for monitoring the trial that are optimal for the design.

Work Package 4: The Ethics Agent: this agent will be responsible for reviewing the protocol and appropriate sections required for typical research, ethics board submissions as well as health system access. It will integrate with current active research, ethics board electronic systems, such as CTO, CanReview and REBX, and fill in the appropriate sections derived from the protocol and other sources. It will further have a subject agent specifically designed for informed consent forms which will utilize templates provided by each of the different ethics boards for the appropriate situation: main consent, genetic consent, biomarker consent, long-term linkage consent etc. These templates will pre-populate the agent based on the appropriate jurisdiction and regulatory requirements.

Work Package 5: The Regulatory Agent: This agent will be responsible for identifying the appropriate regulatory bodies that would have oversight and insight into the clinical research. This could include but are not limited to health Canada, the FDA, GCP/ICH as well as individual jurisdictional requirements. It will further design and develop other required documents, such as CVs, delegation logs, and assist in the identification of the appropriate SOP's required to operate a RCT of this nature.

Work Package 6: The Budget and Contracts Agent: This agent will be responsible for designing and developing budgets based on the protocol developed by the protocol agent. It will refine the budget based on uploaded fair market value of tests available in several jurisdictions as well as recently funded RCTs from CIHR, as well as industry standards. The budget can also be refined further for the amount of FTE required by different individuals such as project managers, study coordinators, research associates, biostatisticians etc. The budget module will also be enhanced to calculate values necessary for submission to several agencies, such as CIHR or other funding bodies. This will connect in with a contract agent which will utilize templates developed by the ACT consortium grant (act-aec.ca). These templates are currently being deployed across Canada at the research-intensive universities as well as community-based research sites.

Each of the Work Packages will follow a standardized methodology. Team members are identified by content expertise, and assigned to one or more work packages depending on the timeline and prior developments. The Work Packages will identify the ‘map’ of issues or opportunities, the background knowledge or templates needed, and the output preferred. The test environment will then be created to utilize what has been developed and iterative design will occur.

Key steps will include overall architectural design of the core components and the framework, development of system prompts including roles and reasoning as well how the potential tools available will be integrated into the prompts. The agents will be designed (where appropriate) to interface with LLM, APIs and other tools, and also with strategies that break down the complex tasks into manageable sub-tasks. Most of this will be via python programming although other programming languages will be used. Finally, evaluation and testing will be done, using appropriate metrics and with human evaluations for quality, utility and alignment. Safety considerations will be included as per prior work. Iteration, optimization, updates and fine-tuning will be done alongside considerations of monitoring and ensuring adequate documentation allows for further open-source deployment. This development process is highly domain-dependent— agents require additional emphasis on safety, privacy, and validation compared to agents for other applications.

Key Outcomes

In developing CRAIDL, we will create an efficient and effective RCT structure that uses cutting-edge AI first tools on every aspect of a RCT, from idea generation to knowledge mobilization. In order to benchmark success, the following outcomes and benchmarks will be considered:

1. Create an ecosystem where a RCT can be developed and deployed via an AI-first approach;
2. AI agent for each part of a RCT that can be deployed ‘off the shelf’;
3. Make CRAIDL available to attract RCT projects, including R&D of industrial partners;

4. Meet or exceed quality, safety and regulatory metrics required as a sponsor of RCTs via deployment of AI tools;
5. Benchmark RCT design through deployment such that we can go from idea to site within 4 weeks.

NFRF Program Fit: High Risk, High Reward

High reward: Hypotheses are tested in RCT most effectively in order to provide the highest level of evidence to inform clinical practice and the backbone for clinical decision-making across all health disciplines. However, RCTs are complex scientific experiments that engage health systems, people and an array of operational, regulatory, institutional and investigative teams. As RCTs have evolved, the ability to design, deliver and disseminate trial results has increased in complexity and cost while challenging the capacity to deliver timely scientific results to Canadians (and globally). Much of RCTs remains manual, subjective, and is inefficient both in the design and the delivery of the RCTs. In order to move beyond subjective and manual processes, the time is right to disrupt the process starting at the beginning: the idea. If we are able to accomplish all or part of the agentic design via an open architecture and methodology, we can design and deliver more efficient and effective RCTs for Canadians. To this date, whereas industrial and academic partners have focused on single areas (e.g. LLM for patient finding or event adjudication) these have remained as a single task and disconnected from all other potential to automate and coordinate RCTs. Measured in either FTE of RCTs teams, the current expenditure is measured in multiple of 100s of hours of FTE just in the design phase, before a patient is even enrolled. Creating a system that can go rapidly from idea to first patient enrollment will shift the field dramatically. The most compatible comparator is the RECOVERY trial, which was able to write the first draft of a protocol over ~3 days, and enroll the first patient within 9 days of that protocol.[4] That innovation took full teams across the UK many 1000s of human FTE hours to achieve and only on a platform of urgency that has not been re-created since. It additionally was a large simple RCT on the backbone of an established RCT network, whereas most RCTs are not either large and simple or built on a network. Additionally, it had a limited regulatory framework – most was effectively waived. CIHR funded networks cannot efficiently design and deploy RCTs – they are a great source of ideas and connected networks but cannot do as above described.

High risk: Agentic design has never been done before in RCTs from beginning to end. While the concept appears feasible and agentic design has rapidly evolved, our team has to bring together several disparate fields. Ground truth information to serve for all agents may be protected in some cases however with greater open-source requirements of all trials, this is now de-risked. Additionally, we have to create an interface that a typical end-user (clinical researcher) can utilize to create the material that can be refined further. The PI and team are faculty at the CVC (thecvc.ca) where we design, operationalize and disseminate clinical trials, and thus have access to > 50 trials (covering all Work Packages) of different design and funding.

Interdisciplinary nature: All faculties of the College of Health Sciences at the University of Alberta participate in RCTs, either at the design level or at the site level, or in the community. Some of the science done in the health sciences at any university could be further enhanced by encouraging swift translation into a RCT to enhance hypothesis testing. Many of the current ideas may simply be stopping short of impact due to the lack of infrastructure or know-how to do RCTs, and others due to perceived or actual operational or regulatory barriers. The CRAIDL will draw on a wealth of knowledge from many disciplines to suggest study design and protocols. None of this will be possible without the collaboration of computer scientists, regulatory experts, research ethics, and health sciences of different professions (e.g. medicine, physiotherapy, nursing, dietetics).