Assurance Case Design for Computer-Aided Clinical Trials
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Introduction: Despite the cost, many clinical trials (CTs) fail to demonstrate the desired effect, resulting in a waste of valuable resources and endangering patients who participate. A computer-aided clinical trial (CACT) is defined as a process in which high-level models of the human physiology are used to evaluate device performance on virtual population of simulated endpoints in the planning, conduct and analysis of a clinical trial. Acceptance of results from a CACT as regulatory-grade evidence requires clear communication about the scope and assumptions under which the CACT results were derived.

Materials and Methods: The assurance case is an established methodology for argument that a system satisfies a claim and has been accepted by regulatory organizations such as the FDA as a possible format that manufacturers can demonstrate the validity of safety claims for infusion pumps in premarket submissions. The pre-clinical simulation stage of a CACT is depicted in Fig. 1(a) where a physiological model is used to generate a virtual cohort of simulated endpoints which are used to evaluate a device model. This process can be abstracted as a system for which the inputs are the simulated endpoints and the output is the evaluation result (Fig. 1(b)). The assurance case framework is used to decompose the claims of the CACT about the target medical device, while unambiguously stating the scope and assumptions of the simulation, such as the method of analysis, the range of parameters for generating physiological signals, etc., through context nodes.

Results and Discussion: In our previous work we have developed a statistical framework to evaluate the robustness of CACTs and here we present the assurance case towards FDA compliance. Fig. 2 depicts the abridged version of the resulting assurance case for the pre-clinical simulation shown in Fig. 1(a). The case is presented for a CACT comparing the performance of two ICD discrimination algorithms. In this case, the top-level claim (G_1) is that the CACT is able to detect a significant different in treatment effect. The context of the top-level claim is stated in context nodes (C_1, C_2, C_3). As in C_6, the structure is modular and can refer to other assurance cases. Additionally, key aspects, such as model validation criteria (C_6), can be agreed upon between developers and regulators and stated clearly in the case.

Conclusions: Incorporating computer modeling simulation results device evaluation in the context of the clinical trial context has the potential for substantially improving the efficiency and success of the current standard. The assurance case for CACTs presents a concrete, unambiguous arguments about the context from which simulations results are derived. This allows for proper consideration by regulatory officials leading to acceptance of simulation results as regulatory-grade evidence for medical device safety and efficacy.