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General Protocol for Ethical Conforming Development for Non-Invasive Blood Biomarker Measurement Optical Device

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Abstract. The new Indonesian national regulation for medical device evaluation necessitates the modification of current best practices for solution development. This article describes our current protocol for medical device development and evaluation. We have combined best practices from Simplified Pressman Standard and Indonesian Technology Readiness Level and Clinical Trial Regulation as a base for our medical device development and evaluation methods. Settings. This protocol is currently evaluated by "Konsorsium Riset Alat Ukur Haemoglobin, Kadar Gula (Glukosa dan HbA1c) Non-Invasive" between IPB University, Agency for the Assessment and Application of Technology, and PT Tesena Inovindo. This article is a preposition article developed from literature research and currently evaluated in three years of research in the consortium. We have developed a three-phase protocol, consist of technology, product, and market phase. This article describes in detail for each point for this protocol, using our current non-invasive blood glucose and Haemoglobin level medical device as an example. The technology phase includes primary literature and lab review for technological units for the non-invasive medical device. The product phase describes best practices for laboratory examination for medical device development in the research stage. The market phase describes best practices for medical device development for consumer usage. We are currently evaluating our protocol. and shall report the evaluation within three years.

INTRODUCTION

All medical devices require a specific level of clinical investigations [1]. There are four phases of medical devices trial, Pilot, Feasibility, Pivotal, and Post Market Phase, which are roughly equivalent to drugs clinical trial phases [2,3]. The clinical trial could take up between three to seven years [4], under the jurisdiction of the National Health Ministry or the equivalent governing body [5,6]. The non-invasive blood-biomarker-level measurement device is a

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class II to class III medical devices. The device malfunction could cause false diagnoses that can indirectly harm the patient [7]. ClinicalTrials.gov currently lists 27 non-invasive glucose trials, ten with completed status. However, none has disclosed their results [8–17]. ClinicalTrials.gov also lists 67 non-invasive haemoglobin trials. There are 28 trials which already completed, and seven have been disclosing their results [18–24].

Medical device success in a clinical trial is directly related to its technology readiness level. This level shows the maturity of a technological unit before acquisition for regular use [25]. The article describes the maturity in nine-level, from preliminary concept to proven solution in the operational environment [26–28]. The methods originally developed by NASA for its technology evaluation methods [29–31]. The level described the fidelity of assessment and built for the technology [32], but not its maturity as a system [33].

Sound development methods are essential for medical device development. However, the unique paradigm in medical device development and clinical trials demand a different approach in solution development [34]. The manufacturers of medical devices are responsible for the safety and effectiveness of their products [35]. The clinical trial obligation for medical device development necessitates an iterative approach [36–39]. That means the traditional model should be modified [40,41]. Furthermore, medical device development involved many stakeholders in nature [42].

This article describes our current protocol for medical device development and evaluation. We have developed this protocol taking all three described elements into consideration.

METHOD

We have combined best practices from Simplified Pressman Standard 40 and Indonesian Technology Readiness Level and Clinical Trial Regulation as a base for our medical device development and evaluation methods. Articles are indexed using both Docear and Zotero [43,44]. Relevant article gathered from Google Scholar, Scopus, and MedLine, as well as ClinicalTrials.gov [45].

RESULTS AND DISCUSSION

General Protocol

We have matched our general protocol to the technology readiness level and clinical trial phase (TABLE 1). We have mapped most of the protocol details from each detail needed in the Technology Readiness Level. We have added Point 1.1 to attend the need for legal protection for derived technology and to prevent a subsequent dispute between stakeholders.

TABLE 1. General Protocol for Non-Invasive Biomarker Level Measurement Device mapping against Technology Readiness Level and Clinical Trial Phases

Technology Readiness Level [28]	Clinical Trial Phase [3]	General Protocol for Non-Invasive Biomarker Level Measurement Device	Detailed Protocol
1. Basic Principles Observed 2. Technology Concept Formulated	Phase 0	Pre Protocol Preparation	0.0. Research Team Establishment 0.1. Literature Review 1.1. Intellectual Property Agreement 1.2. Blood Model Characterisation
3. Experimental Proof of Concept 4. Technology Validated In Lab	Phase 1 Pilot	Phase 1 Prototype Simulation	1.1. Intellectual Property Agreement 1.2. Blood Model Characterisation 1.3. In Vitro Trial Protocol 1.4. Simulation Prototype 1.5. Technological Unit Evaluation 1.6. Simulation Prototype Evaluation 1.7. Registered Patent 1.8. International Publication Draft

Technology Readiness Level [28]	Clinical Trial Phase [3]	General Protocol for Non-Invasive Biomarker Level Measurement Device	Detailed Protocol
5. Technology Validated In Relevant Environment 6. Technology Demonstrated In Relevant Environment	Phase 2 Feasibility	Phase 2 In Vitro Prototype	1.8. International Publication 2.1. Clinical Trial Protocol 2.2. In Vitro Prototype 2.3. In Vitro Trial 2.4. Registered Patent 2.5. International Publication Draft
7. System Prototype Demonstration In Operational Environment 8. System Complete and Qualified	Phase 3 Pivotal	Phase 3 In Vivo Prototype	2.5. International Publication 3.1. Product Certification 3.2. Economics Analysis 3.3. In Vivo Prototype 3.4. In Vivo Clinical Trial 3.5. Registered Patent 3.6. International Publication
9. Actual System Proven in Operational Environment	Phase 4 Post Market	Phase 4 Post Market	3.6. International Publication 4.1. Post Market Improvements

Note. Double listing of 1.1, 1.2, 1.8, 2.5, and 3.6 are intentional.

Protocol 0.0. Research team Establishment

The research team in minimal should consist of the developer team, clinical trial team, and business and legal team. The developer teams should consist of members from diverse background, as medical devices development are mostly trans-discipline. As a national policy, there should be involved in an educational hospital.

Our current consortium is consists of members from IPB University, Agency for the Assessment and Application of Technology, and PT Tesena Inovindo. We are currently in talks with Rumah Sakit Umum Daerah Tangerang for a possible partnership.

Protocol 0.1. Literature Review

The researcher should start by making a literature review on the chosen blood biomarker level. We recommend PRISMA as reporting guidance [46–55]. The reviewer should use peer-reviewed articles as well as clinical trial reports. They should gather new and up to date as well as a higher level of evidence [56]. We recommend Zotero and Docear for indexing service [43,44]. Approval from the ethical committee maybe not needed, but the researcher should consult the local ethical committee.

Protocol 1.1. Intellectual Property Agreement

Agreement on how intellectual property that the consortium shall create should exist before undergoing the research. All the stakeholders should be present for the agreement declaration. Lembaga Pengelola Dana Pendidikan (LPDP) has reported that this agreement became mandatory due to several post research disputes from past research consortium.

Protocol 1.2. Blood Model Characterisation

One problem in blood biomarking research is, how diverse and contradictive each research result is [57–59]. This necessity that the researcher should verify the result with his observation or experimental study. The researcher can use IMRAD as a reporting guide 60, but CONSORT is preferred [61–63]. One standard method is to observe the blood model or extracted blood from human volunteers using conventionally accepted gold standard methods [64–66]. Ethical clearance and clinical trial registration are mandatory if the research involves human or animal subject [67].

Protocol 1.3., 2.1. Clinical Trial Protocol

Ethical clearance and clinical trial registration should be proposed at least six months before each human experiment. The researcher should do both registrations before all experiment that involves human or animal subject [65,67]. Please consult to local ethical committee or authority for the detailed procedure.

Protocol 1.4., 2.2., 3.3. Prototype Development

The prototype of a non-invasive measurement device should run in an iterative manner [40,68]. The developer should at least built three prototypes. The prototypes are simulation, in vitro, and in vivo prototype. Medical device manufacturers should be involved in each prototype iteration.

Protocol 1.5., 1.6., 2.3., 3.4. Prototype Evaluation

There at least three evaluations should be made. The evaluations are model simulation, in vitro, and in vivo clinical trial. We recommend doing simulated evaluation using blood model [64]. The blood may be in artificial human appendage. Both the in vitro and in vivo evaluation involves human subject, but the first one involves blood extraction [69]. The in vitro and in vivo evaluation should run in an educational hospital 6. In those trials, the research should compare the prototype against the current gold standard [65]. The researcher should make the report should in CONSORT [70–73].

Protocol 1.7., 2.4., 3.5. Registered Patent

We recommend registering a patent for each developed prototype. The patent is to protect the ownership of design within national jurisdiction. The ownership of each prototype design is dependent on the previous consortium agreement.

Protocol 1.8., 2.5., 3.6. International Publication

We recommend reporting each evaluation result in both clinical trial index and reputable journal [45]. Which indexer to use is dependent on the national ministry of education and research policy. Each publication should conform CONSORT reporting guide [70–73].

Protocol 3.1. Product Certification

Resulting in vivo prototype should undergo product certification to local authority [6]. Product certification is to make sure the conformance of the prototype to the national standard. Consult to the national ministry of health for current detail.

Protocol 3.2. Economics Analysis

The analyst should make the economic analysis for the prototype in each iteration. However, it may only be relevant to the end product. The analysis consists of customer needs, market needs, business investment, and business plan [74]. The reporting guide is dependent on medical devices manufacturer standards.

CONCLUSIONS

We have described our protocol. This protocol is currently evaluated in Konsorsium Riset Alat Ukur Haemoglobin, Kadar Gula (Glukosa dan HbA1c) Non-Invasive" between IPB University, Agency for the Assessment and Application of Technology, and PT Tesena Inovindo.

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The authors declare no competing interests.

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