# LONGITUDE PRIZE

## FREQUENTLY ASKED QUESTIONS ON LEVEL OF DEVELOPMENT

Frequently asked questions on the level of development required of applicants when applying to win the Longitude Prize in reference to the new in-vitro diagnostics regulations for the European Union

# PURPOSE OF THIS DOCUMENT

All competitors who submit an application to win the Longitude Prize (LP) must be able to demonstrate they have reached the level of development as stated in the Longitude Prize Rules.[1]

Before entering the Longitude Prize you must have produced at least three functional test units. It must be a design-locked, optimised prototype which has undergone performance evaluation in preparation for regulatory approval.

You must submit laboratory data that demonstrates the accuracy and safety of your test. In addition, you must submit qualitative data that indicates that your test will have adequate clinical utility in your chosen clinical pathway(s). Published data is preferred.

These frequently asked questions (FAQ) have been compiled to address questions commonly received by the Longitude Prize management team in reference to the level of development needed.

These FAQs are written in reference to the new EU IVD regulations as it is expected that a successful Longitude Prize winner would submit for registration in Europe.

# TARGET AUDIENCE

Applicants for the Longitude Prize who have questions on the requirements for the level of development of their IVD when applying to win.

Applicants for the Longitude Prize who are planning to submit for registration in the EU under the new IVD regulations.

# LONGITUDE PRIZE

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# PART 1
# TERMS USED IN THE LONGITUDE PRIZE RULES

## 1.1 In the context of the Longitude Prize, what is meant by prototype?

A prototype in the context of the Longitude Prize is a finished device that is ready to be manufactured on a commercial scale.

## 1.2 What is an optimised prototype?

The performance of the device has been optimised during development to achieve the best possible outputs given current state of the art and knowledge, without compromising its safety.

Performance covers all the desired outputs of the device including analytical sensitivity, specificity and reliability of testing, as well as practical matters like time to result, simplicity of use, storage conditions, packaging and transport conditions and shelf life.

Optimisation of a device is usually scheduled once the design of the device and the user protocol are established. This is done by methodically testing and adjusting the device, user protocol and reagents together.

## 1.3 What does design-locked mean?

Design-locked means that all specifications of the design of your device have been decided and are final. Design-lock occurs after the optimisation stage when the performance of the device is considered optimal and is now ready to be tested in the clinic. At design lock, all reagents, consumables, materials, equipment and software algorithms have been fully described/defined.

## 1.4 Can a change be made to the design before, during or after performance testing for regulatory approval?

This is not recommended.

Changes made to the design during or after performance testing could render all or some of your analytical and clinical performance data invalid.

Changes made before testing starts are possible but in effect you are unlocking the design. The necessary steps to lock down the design again should be repeated, a risk analysis conducted on the impact of the change on all data gathered during development and optimisation, and any repeat testing completed.

A change is acceptable if it clearly has no impact on form, fit or function. This is documented in a risk analysis.

## 1.5 What does functional test unit mean?

A functional test unit is another term for the finished device or the design-locked prototype.

## 1.6 How should the functional test units be manufactured?

The functional test units should be manufactured following final manufacturing instructions including all in-process and end of production quality control testing, and all data and activities should be detailed on manufacturing records.

## 1.7 Where should the functional test units be manufactured?

Ideally, the functional test units should be manufactured at the site that will produce the commercial product.

It is possible to make these units at a different site if the manufacturing environment, procedures, processes and forms are identical to those that will be used for commercial production.

Note that if the IVD device is manufactured for commercialisation at a different site to the one that manufactured the product used for performance evaluation and testing, then production transfer validation and equivalence data will be required. Please note that this is considered a significant design change.

## 1.8 What is meant by laboratory data?

Laboratory data in this context means analytical performance data.

These are data that have been generated using your design-locked prototype. It is expected that you will have collected all the analytical data that would be required for European registration to support your application for the Longitude Prize. Analytical data support the validity of your clinical results, and the confidence the judges will have in your performance claims. The detail of analytical performance data required for EU registration is outlined in Part 4.

## 1.9 What makes an IVD a point-of-care device?

Point-of-care IVD devices are devices that are designed to be used in the near patient setting. Near patient settings include doctors' offices, emergency departments, pharmacies, walk-in health clinics, field hospitals and remote primary care outreach settings.

The characteristics of a point of care IVD device include: simple sample collection and minimal processing; rapid time to result; small footprint of equipment; portability; non-reliance on uninterrupted electricity, flexible transport and storage conditions, heat-stable reagents and easy to use, minimum training required for a professional person.

# PART 2
# OPTIMISATION OF AN IVD

## 2.1 Why is this needed?

Once a device has been developed to the point where it is working as expected, and looks likely to meet the product design goals/specifications, the optimisation step investigates systematic changes to the design or protocol for use to achieve the best possible performance.

Optimisation is not always focussed on clinical performance (e.g. improving sensitivity/specificity). It may focus on simplifying the test – reducing the number of steps or operations required in the protocol for use – or replacing a step that is identified as the potential largest source of human or technical error.

Inputs into the optimisation phase may include, amongst others, product design goals, issues arising from the risk analyses, practical experience from the development laboratory, human factors (see below) and other European regulations and directives.

## 2.2 How should this be documented?

That is up to individual organisations, there is no pre-determined format. However, as these data support decisions taken to lock down the design, the test protocols and reports are a critical part of your design control and technical documentation.

## 2.3 How much optimisation is required?

That is up to the individual organisation to determine when the optimisation phase is complete. The questions an organisation could ask itself might include:

- ✓ Have we achieved all our design goals and/or specifications?
- ✓ If we have been unable to achieve one or more of them, have we got close enough that the device is still clinically and commercially viable?
- ✓ Have we reduced all the risks associated with the use of the device as much as we can through our design and development?
- ✓ Have we got enough data to demonstrate that in the hands of our intended user, our device should deliver the performance expected?

This type of questioning will help you decide if optimisation is complete and the device design can be locked down, ready for its final phase of testing.

## 2.4 What role do Human Factors have to play?

A critical role. There is a General Requirement in the In Vitro Diagnostic Medical Device Regulation (IVDR)[2] that manufacturers will take Human Factors into consideration when designing the device. This includes active consideration of the ergonomics of the design. It also includes consideration of the mental and physical capabilities of the likely user. For example, if the device is hand-held – how was it designed for weight, size and shape? Whose hands were used as models, and how similar will they be to the intended user hands? Will the device be held for a period of time? Does the protocol require a level of dexterity likely to be beyond the average field worker? Does the visual display require perfect vision and good lighting?

There is a harmonised standard on usability engineering[3] that is the go-to document to help manufacturers demonstrate compliance with this General Requirement.

## 2.5 What is the role of other European Regulations and Directives?

Some EU Regulations[4] have a ban on certain substances being used in products to be placed on the European market, or if not banned outright, have restrictions on the quantities that may be imported annually into the EU, or require a licence to use them. If the device has been developed and includes any of these banned or restricted substances, optimisation is the last opportunity to design them out.

# PART 3
# PERFORMANCE EVALUATION

## 3.1 What is meant by Performance Evaluation?

Performance Evaluation (PE) is the ongoing process of gathering all clinical evidence needed to demonstrate that the IVD meets the requirements of the IVDR. There are three distinct pillars of clinical evidence, and each of them needs to be addressed in order to demonstrate that adequate performance evaluation has been conducted.[5]

The three pillars are: scientific validity (Part 3.2); analytical performance (Parts 4.2 to 4.4); and clinical performance (Parts 4.5 to 4.7).

A PE Plan that details the approach that will be taken to gather the data supporting these three components of clinical evidence, should be written. This PE Plan is a mandatory document for the IVDR.[6]

A PE Report is also required, summarising the outcomes of the PE Plan and drawing conclusions from the three components of scientific validity, analytical and clinical performance.

Performance evaluation is continued throughout the product lifecycle and does not finish at the point of product launch. For organisations who intend to commercialise their device themselves, the PE report should also refer to the Plan for Post Market Performance Follow Up.

## 3.2 What is required for the scientific validity report?

The scientific validity report should clearly demonstrate the scientific logic behind the principles of the test and its link to the clinical claims, including the target test population. The data supporting this scientific argument may be drawn from a combination of the literature, expert opinion, proof-of-concept laboratory or animal data, competitor product publications or other similar sources.

If the biomarker in question is well established and is being measured in its established physiological pathway, the scientific argument may be largely based upon existing literature. A new biomarker or one which is being measured in an unusual physiological process may require more laboratory data to explain its relevance.

# PART 4
# ANALYTICAL AND CLINICAL PERFORMANCE DATA

## 4.1 What is the difference between analytical and clinical performance data?

Analytical data focus on the performance of the test in measuring the analyte, biomarker or measurand in clinical or spiked clinical samples.

Clinical performance data focus on the performance of the test in the intended use population when used by the intended users in the intended use setting. This is a requirement of the EU IVD Regulation.[7]

## 4.2 What analytical performance data are required?

The IVDR states in a General Requirement that analytical data will be required for the following device test performance parameters:

- ✓ Analytical sensitivity;
- ✓ Analytical specificity;
- ✓ Trueness (bias);
- ✓ Precision (repeatability and reproducibility);
- ✓ Accuracy (resulting from trueness and precision);
- ✓ Limits of detection and quantitation;
- ✓ Measuring range;
- ✓ Linearity;
- ✓ Cut-offs;
- ✓ Criteria for specimen collection and handling;
- ✓ Identification and control of known relevant endogenous and exogenous interfering substances;
- ✓ Cross-reactions.

It should be noted that if any of these parameters are considered not relevant to your device, the lack of data must be justified.[8] The appropriate place to document this justification could be the PE Plan.

## 4.3 What samples are acceptable?

Analytical data can be generated using a mixture of sample types:

- ✓ Well characterised clinical samples with a documented history of their collection, handling and storage;
- ✓ Well documented panels of artificially contrived samples or spiked samples;
- ✓ External Quality Assurance (QA) panels or reference materials.

Risk analysis can be used to identify which analytical tests can be conducted using spiked or artificial panels, and which must be done using representative clinical samples.

## 4.4. How much analytical data needed?

The PE Plan will identify the analytical performance parameters required and should include a discussion of statistical methods and tools that will be used to establish the testing programme and analyse the data. There are some guidance documents issued by Clinical & Laboratory Standards Institute (CSLI)[9] that provide a template for some of these analytical test performance parameters, including recommended sample sizes. These guidance documents are widely recognised by the industry and the regulators.

Analytical data are required to support each sample type that is proposed to be used. This includes collecting datasets for whole blood, plasma and serum. Additionally, if multiple instruments are to be permitted, analytical data will be required to demonstrate that the different platforms support the test device and do not affect the test result.

In addition to the list of device performance parameters above, data are also required to support stability of the device during transport, to support the recommended storage conditions, to establish the device shelf life and if appropriate, open-box shelf life.[10]

IVDR General Requirement 9.2 also stipulates that the device test performance achieved at the beginning of its shelf life must not have deteriorated by the end of shelf life. To achieve this, devices placed on stability should undergo selected analytical performance testing near the end of shelf life as well as fresh off the production line.

At the time that a device is submitted for consideration by the Longitude Prize judges, it is not expected that the longitudinal shelf life stability studies will be complete. At the time of submission, the minimum requirement is that they are underway. It should be noted that for EU registration and CE marking purposes, IVD shelf life is established on the basis of real time stability data and may be backed up with accelerated data, and that accelerated stability studies are not appropriate for every IVD.

In addition to the stability and transport data, if the device requires the use of controls or calibrators to ensure a valid result the metrological traceability of values assigned to calibrators and/or control materials must be demonstrated, and if necessary reference methods validated.

## 4.5 What clinical performance testing must be done?

Clinical performance testing will always be carried out using clinical samples from the intended use population. The intended use of the test will dictate which clinical performance is most appropriate.

Diagnostic sensitivity and specificity are the most commonly quoted, and it is likely that the following will be required for the Longitude Prize:

- ✓ Diagnostic sensitivity;
- ✓ Diagnostic specificity;
- ✓ Positive predictive value (PPV);
- ✓ Negative predictive value (NPV);
- ✓ Likelihood ratio;
- ✓ Expected values in normal and affected populations.

PPV and NPV must take prevalence of disease into consideration and are not simply deduced from a small patient study. In common with the Likelihood Ratio, they are a measure of probability of disease present or absent.

Expected values in the normal and affected population are important if the analyte or biomarker being measured by the device is present in the normal population. The normal range needs to be established to understand the cut off (or overlap) between normal and affected populations. The narrowness of the cut off or the degree of overlap is of particular interest when a device is being employed at an early stage of disease.

Depending upon the analyte or biomarker, the normal ranges may vary in different ethnic groups or by gender or age.

The device undergoing evaluation should be compared to another diagnostic test or procedure that is considered a 'Gold Standard' in the diagnosis – i.e. will give the 'truth'. A 'Gold Standard' can be a combination of test results if that reflects the state of the art in clinical diagnosis for the clinical condition. Choice of comparator test(s) is a critical part of study design.

If a comparator is selected that is not recognised as a 'Gold Standard', the statistical guidance that is published by the US Food and Drug Administration should be consulted as the study may not be considered an adequate design of diagnostic sensitivity or specificity.[11]

## 4.6 What clinical samples are acceptable?

Banked clinical samples are acceptable if the clinical study protocol can demonstrate that no bias is introduced into the design, and the outcome of the analysis will be no different to prospectively collected fresh samples.

Samples should be collected and used from the type of patient for which the test is intended, to generate context-appropriate evidence.

Clinical samples that have been retrospectively collected and banked at low storage temperatures (fridge or freezer) can be used. A cooling-warming or freeze-thaw cycling study is required to demonstrate the low temperature storage has had no effect on the sample and the test result.

Samples that have been archived for some time, possibly collected for an earlier completely different study may also be used if a study has shown no effect of long-term storage at low temperature and there is

adequate information about the storage conditions of the samples. Freezer monitoring records or graph traces would be commonly expected.

Clinical samples that have been in low temperature storage for a prolonged period where the conditions of storage cannot be assured are not recommended to be used.

Leftover samples – where the sample was drawn for a routine diagnostic test and the excess sample volume is adequate for the test device may be used, if all other sample criteria are met. However as clinical data may be required, and clinical records may need to be consulted, informed consent should be obtained.

Archived and long term banked samples that were not collected retrospectively for the study must be justified in terms of their appropriateness for the study in hand. For example, are they representative, not just of the clinical condition but also of the co-morbid illnesses and current medical therapeutic treatments?

## 4.7 How much clinical performance data are required?

The sample size must be statistically generated for each clinical study undertaken to ensure the analysed data and reported outcome has statistical validity.

The number and complexity of studies required will be determined by the product claims. The more claims that a manufacturer wishes to make, the more that will be required to support them. If the claims include multiple sample types, then clinical data for each sample type will be required, and statistical justification for the numbers of each sample type tested should be provided in the PE Plan.

## 4.8 Point of Care/Near Patient Testing Device Evaluation Study

A user evaluation study must be conducted.

The evaluation study will take place in settings similar to the intended use environment, and the device will be used by the device target users, on the target population described in the intended use statement.

Training on the use of the device that is given to the users in the study must be the same as the training planned for commercial product users.

The evaluation study will be run using the final draft of the instructions for use, and the study is intended to confirm that the performance characteristics of the device are not affected when the device is used under normal conditions.

As part of documentation review for EU product registration, the Notified Body will be looking for evidence that this evaluation has been completed.[12]

## 4.9 Do clinical performance data have to be gathered in a prospective clinical study?

For product registration in compliance with the IVDR, there is no requirement or obligation to conduct a prospective clinical study to validate your clinical performance claims. However, as noted in Part 4.8, a user evaluation study must be conducted to demonstrate that your clinical performance can be achieved by your intended users under normal conditions of use. The samples used are likely to be gathered prospectively and must represent the intended use population (see Part 4.6).

Prospective clinical studies will be required if your freeze-thaw studies show that your sample type is hard to collect and store ahead of testing, or if you require clinical follow up for any period of time.

# PART 5
# CLINICAL UTILITY

## 5.1 What is meant by clinical utility in the context of the Longitude Prize?

Clinical utility in the context of the Longitude Prize is the prevention in the rise of resistance to antibiotics. As an outcome of a clinical study, this would be difficult for a diagnostic device to demonstrate and therefore certain surrogate end points should be considered. These could include:

- ✓ Safely reducing use of antibiotics;
- ✓ Prescribing the most effective and where possible narrowest spectrum antibiotic as a first line treatment;
- ✓ Safely reducing the number of antibiotic doses in a course for effective treatment.

Any of these surrogate outcomes would contribute to the overall clinical aim of the Longitude Prize.

## 5.2 Is a clinical utility study required?

No, it is not a requirement that a clinical utility study is conducted as part of a Longitude Prize submission.

## 5.3 What is meant by qualitative data supporting clinical utility?

Conclusions drawn from qualitative data will by definition be less precise than those drawn from quantitative data generated by clinical utility studies. However robust qualitative data can be generated if the research methods maintain scientific rigour and objectivity. Consequently, the methodology used must be comprehensively documented for review by the Longitude Prize judges.

Based upon your clinical performance data (section 4.5), it is expected you will be able to model the impact of your test within your selected clinical pathway and provide qualitative evidence that your test will have some utility.

## 5.4 How can I model clinical utility?

A diagnostic paper tool (questionnaire) could be developed that interrogates change in prescribing behaviours at the actual decision points in the clinical work up of a patient. In order for a treating clinician to make an informed choice (and not a conservative status quo decision), the clinical performance characteristics must be known. For example, outcome could be:

- ✓ Decision to not prescribe an antibiotic where default would have been a prophylactic broad-spectrum course of antibiotic;
- ✓ Decision to prescribe a specific and tailored antibiotic as first line instead of routine broad spectrum.

## 5.5 Is this the same as an economic or cost-efficiency model?

No. It is important to remember your outcome here is a reduction in use of antibiotics or reduction in inappropriate use of antibiotics. Neither of these two outcomes may deliver cost efficiencies as antibiotics tend to be less expensive than medical intervention.

## 5.6 Is ethical approval required to administer this questionnaire?

Possibly. It is required in the UK, and groups would need to consult their local ethics committees to be aware of their responsibilities. As there is no patient involvement and no clinical impact on the patient, it represents an administrative delay only.

## 5.7 Are there alternatives to the questionnaire?

Yes. For example, you could consider a literature-based model on the impact of your test by using conservative estimates for clinical decision making based upon published data or models that could be extrapolated to your clinical pathway.

Another approach could be a survey, based on the questionnaire, but not during clinical workup. The survey could be administered as a number of hypothetical situations to a wide number of clinicians. This would not require ethical approval however the outcome could be considered positively biased in favour of the test as decisions made with no patient involvement are generally less conservative, and therefore the reporting of these qualitative data should take that into consideration.

## 5.8 What is meant by clinical utility in the context of an IVD registration in Europe?

Clinical utility has no actual definition in the IVDR.

It has been taken to mean that the analyte, biomarker or measurand that your device has been designed to measure is accurately reported by your device when the device is used as intended, and under normal use conditions.

# PART 6
# OTHER EU REGISTRATION-READY REQUIREMENTS

## 6.1 Technical documentation

Several documents and records have been referred to within this FAQ that are a critical part of the technical documentation required by the IVDR. However, there are many more not covered in this document. It is outside of the scope of this document to list everything that would comprise technical documentation for a device to be CE marked in Europe, and the interested reader is referred to Annexes II and III of the IVDR. In addition those listed in these two Annexes, there are additional documents required to support your quality system and your risk management files.

## 6.2 Will I need a Quality Management System (QMS)?

Yes. All IVD developers are required to have a QMS tailored to their activities, their proposed status as legal manufacturer, and their plans for product commercialisation.

If the device will be licensed to a third party who will complete the regulatory registration process, be the legal manufacturer and take over all responsibilities for commercialisation, you need technical documentation that demonstrates you have followed the design control requirements of ISO 13485 Section 7. This covers product realisation from concept through to production. You will also need to implement several other parts of the QMS standard including document control, training, corrective and preventive action, control of non-conforming product and management responsibility.

If you intend to be the Legal Manufacturer, all relevant parts of ISO 13485 will apply to you.

## 6.3 When do I need my QMS?

At the earliest possible stage. Design control should be in place from the beginning of design and development.

If design and development has started without a QMS in place, implement it now, and make adjustments to your design and development plans as needed.

## 6.4 What kind of QMS do I need?

ISO 13485:2016 is the quality management system for regulatory requirements for medical devices. This standard is accepted by all EU countries and certification to ISO 13485 will meet all QMS requirements expected by the IVD Regulation (IVDR).

Manufacturers may choose to implement other quality management systems however the onus is on the manufacturer to demonstrate that their preferred solution is equivalent to ISO 13485 and will deliver the requirements of the IVDR.

## 6.5 Am I required to do risk management?

Yes. The IVDR and ISO 13485 both emphasise the importance of incorporating risk management into product design and development and continuing it throughout a product lifecycle.

A risk management file is required by ISO 14971:2012

## 6.6 Why do I need this if I am not registering my product in the EU or UK?

The Longitude Prize will be awarded to a team who has developed a device that will be a point-of-care diagnostic test to help tackle antimicrobial resistance. As the prize is funded by the British Government, there is an expectation that the test will be registerable in the UK/EU, even if by a third party. A test that has been developed but is not supported by a quality management system and has not taken the requirements of the IVD Regulation into consideration is not registerable.

# PART 7
# VERIFICATION TESTING OF A POTENTIAL LONGITUDE PRIZE WINNING DEVICE

## 7.1 Why is verification testing carried out by Nesta?

Nesta reserves the right to ask a third party independent laboratory to verify the performance claims of any device that is a likely contender for the Longitude Prize.

Independent verification of tests is routinely carried out by clinical laboratories when they implement new tests to ensure they can achieve the expected performance characteristics in their own setting.

In addition, the IVDR will require all high risk IVDs to be independently verified by European Reference Laboratories before they are approved for market.

If the package of clinical data supporting the submission contains adequate data collected by a number of laboratories, the verification testing may be waived.

## 7.2 How will this testing be done?

An independent laboratory will develop a statistically robust protocol to verify your clinical performance claims, using your test, following your instructions for use in the target patient population.

## 7.3 What involvement will we have in the development of the testing protocols?

The verification protocol will be supplied to you to review prior to performing the study. This is your opportunity to highlight anything that you know could interfere with the integrity of the study. For example, the study proposes to use banked frozen samples and you have data to demonstrate that frozen samples perform differently to fresh samples.

It is not expected that you will have authors input into the protocol.

## 7.4 What happens if the results of the testing do not verify our performance claims?

An investigation will be held, which will include you, to discover the reason for the discrepancy. A repeat study could be run by the laboratory with the development team as observers. The development team could be asked to perform the study themselves at the testing laboratory facility. If the discrepancy cannot be resolved, and the performance claims have not been verified, the laboratory results will be taken as final.

# PART 8
# USEFUL READING

GHTF/SG5/N7:2012 – Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation

GHTF/SG5/N8:2012 – Clinical Evidence for IVD Medical Devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices

# PART 9
# REFERENCES

1. Page 20 of the Longitude Prize Rules, November 18
2. EU 2017/746 ANNEX I CHAPTER 1 GR 5
3. BS EN 62366 Medical devices – Application of Usability Engineering to Medical Devices
4. Directive 2015/863 Restriction of Hazardous Substances; Regulation 1907/2006 REACH; Regulation 528/2012 Biocidal products. NOTE: this is an illustrative list only. There may be others relevant to an individual device.
5. EU 2017/746 Chapter VI, Article 56
6. EU 2017/746 Annex XIII Part A 1.1
7. EU 2017/746 Annex I Chapter 2 Section 19
8. IVDR Annex XIII 1.2.2
9. The Clinical & Laboratory Standards Institute (CLSI) https://clsi.org/
10. ISO 23640 In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents
11. FDA Guidance on Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests 2007
12. EU 2017/746 Annex IX Chapter II Section 5, or Annex X Section 2.

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October 2019