**Human Reproduction, Vol.25, No.4 pp. 1051–1065, 2010**
Advanced Access publication on January 23, 2010 doi:10.1093/humrep/dep450

human reproduction

REVIEW *Reproductive genetics*

# Accreditation of the PGD laboratory

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Accreditation according to an internationally recognized standard is increasingly acknowledged as the single most effective route to comprehensive laboratory quality assurance, and many countries are progressively moving towards compulsory accreditation of medical testing laboratories. The ESHRE PGD Consortium and some regulatory bodies recommend that all PGD laboratories should be accredited or working actively towards accreditation, according to the internationally recognized standard ISO 15189, 'Medical laboratories—Particular requirements for quality and competence'. ISO 15189 requires comprehensive quality assurance. Detailed management and technical requirements are defined in the two major chapters. The management requirements address quality management including the quality policy and manual, document control, non-conformities and corrective actions, continual improvement, auditing, management review, contracts, referrals and resolution of complaints. Technical requirements include personnel competence (both technical and medical), equipment, accommodation and environment, and pre-analytical, analytical and post-analytical processes. Emphasis is placed on the particular requirements of patient care: notably sample identification and traceability, test validation and interpretation and reporting of results. Quality indicators must be developed to monitor contributions to patient care and continual improvement. We discuss the implementation of ISO 15189 with a specific emphasis on the PGD laboratory, highlight elements of particular importance or difficulty and provide suggestions of effective and efficient ways to obtain accreditation. The focus is on the European environment although the principles are globally applicable.

## Introduction

Preimplantation genetic diagnosis (PGD) is a well-established service provided in many European countries, and the overall high-quality standards are attested by the less numbers of reported errors (Goossens *et al*., 2008; Wilton *et al*., 2009). Nonetheless, a recent European survey demonstrated a shortfall in formal quality assurance in PGD centres. Although some genetic diagnostic laboratories which also offer PGD were accredited or preparing actively, accreditation was rare in dedicated PGD laboratories and IVF laboratories providing PGD (Corvelyn *et al*., 2008).

The development of a comprehensive quality management system (QMS) is a time-consuming process, requiring organization, motivation and investment, which may be particularly daunting and impractical to small PGD laboratories with limited staff. The QMS can be developed and used without entering into the formal process of accreditation; however, the extra investment to achieve accreditation is relatively minor and the benefits considerable.

Accreditation, according to an internationally recognized standard such as ISO 15189 (2007) or ISO 17025, represents the formal recognition of a laboratory's competence and of their compliance to the requirements of the standard (Table I) and is recognized as the single most effective route to comprehensive quality assurance. In Europe, accreditation is provided by the national accreditation body, which should be a member of EA (European cooperation for Accreditation). The detailed procedure varies slightly between accreditation bodies, but typically involves one or more external audits by a lead auditor from the accreditation body and a technical expert, specialized in the discipline.

The ESHRE PGD Consortium and some regulatory bodies (e.g. the Human Fertilisation and Embryology Authority—HFEA—in the UK) recommend that all PGD laboratories should be accredited, according to the ISO 15189 standard: 'Medical laboratories—particular requirements for quality and competence'. In the UK, the HFEA have made this mandatory (HFEA, 2009). Similarly, the Organisation for Economic Co-operation and Development (OECD, 2007) 'Guidelines for quality assurance in molecular genetic testing' state that 'All laboratories reporting molecular genetic testing results for clinical care purposes should be accredited or hold an equivalent recognition'.

**Table I Definitions and comparison of accreditation, certification and licensing.**

| | Definition | Involves | Delivered by |
|---|---|---|---|
| Accreditation | Procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks | Formal recognition by an independent body of technical competence, as well as compliance to a QMS | The 'authoritative body' is the national accreditation body of the country concerned. A complete list for Europe is available at http://www.european-accreditation.org/content/ea/members.htm |
| Certification | Procedure by which a third party gives written assurance that a product, process or service conforms to specific requirements | Assurance of compliance to a QMS, most commonly ISO 9001. The scope is variable but (in contrast to accreditation), there are no formal requirements for technical competence | A country may have many 'third parties' able to provide certification |
| Licensing | The permission, permit from a governmental agency to operate a laboratory | Licensing of health-care facilities is distinct from accreditation and certification and does not necessarily require any evaluation of quality management or technical competence | Usually mandatory and government-imposed |

ISO 15189 was developed from the more general (and more complex) standard for general testing laboratories (ISO 17025). The philosophy is to provide comprehensive cover of medical testing in the pre-analytical, analytical and post-analytical phases, including 'arrangements for acquisition, patient preparation, patient identification, collection of samples, transportation, storage, processing and examination of clinical samples, together with subsequent validation, interpretation, reporting and advice, in addition to the considerations of safety and ethics in medical laboratory work'.

ISO 15189 contains two main sections: management requirements and technical requirements (Table II).

Some of the terms and concepts of the standard may be new or confusing to PGD professionals in the early stages of implementing a QMS (http://www.eurogentest.org/laboratories/info/public/unit1/qmanagement/definitions_v1.xhtml). In this paper, we provide a companion guide to the concepts and implementation of ISO 15189 specifically in PGD laboratories, with the aim of demystifying and clarifying the standards. The reader is encouraged to acquire a copy of the standard for consultation with this guide (www.iso.org).

**Table II Requirements of the ISO 15189 standard.**

| Management requirements | Technical requirements |
|---|---|
| Organization and quality management | Personnel |
| Quality management system | Accommodation and environmental conditions |
| Document control | Laboratory equipment |
| Review of contracts | Pre-examination procedures |
| Examination by referral laboratories | Examination procedures |
| External services and supplies | Assuring quality of examination procedures |
| Advisory services | Post-examination procedures |
| Resolution of complaints | Reporting results |
| Identification of control of non-conformities | |
| Corrective action | |
| Preventative action | |
| Continual improvement | |
| Quality and technical records | |
| Internal audits | |
| Management review | |

# Management requirements

## Organization and QMS (ISO 15189: 4.1 and 4.2)

To achieve accreditation, the PGD laboratory needs a quality manual, quality policy, with specific measures to ensure document control, record control, sample control all of which combine to form the QMS. A QMS is essential for the smooth running and maintenance of quality in PGD (Vendrell *et al.*, 2009). The QMS is essentially the sum total of the quality manual, the procedures, controls and systems in place to ensure quality.

The laboratory must have a designated quality manager responsible for maintaining the quality manual, implementing the quality policy and ensuring the application and development of the QMS. This individual can be full-time, part-time, dedicated to this task alone or sharing the task with other functions or personnel according to the size, scope and resources of the laboratory. However, it is essential that while the QMS is maintained by the quality manager, specific quality-related tasks and activities (writing specific SOPs, audits etc.) are performed by the appropriate and responsible staff. If staff numbers permit, ideally the QM should not be someone involved in the day-to-day clinical operational running of the PGD laboratory. A key aim should be to achieve a sense of involvement, motivation and 'ownership' of the QMS by operational (i.e. non-management) personnel.

A quality plan is generally revised at least annually, outlining the specific targets of the laboratory to improve the quality of its services. These may include: (i) benchmarking against other PGD laboratories (e.g. comparison of turnaround times or numbers of errors and incidents reported); (ii) improvements in areas identified as potential weaknesses; (iii) improvements in designated, pre-agreed quality indicators (see below); (iv) internal targets for test accuracy and new test

development and validation; (v) a list of internal and external audits planned for the year.

An important feature of the QMS is identifying the organizational relationships between the different entities involved in the service (in this case, PGD treatment and diagnostic testing). Since PGD is necessarily multidisciplinary, this aspect of the QMS is particularly important and a lack of clarity in work flows, reporting lines and relationships can lead to poor quality of service despite technical excellence. Moreover, the patient-focused approach, while paramount, is not the only relationship of importance. In PGD, other client–provider relationships exist (e.g. the PGD laboratory has the IVF clinic as its user). To this end, it is critical to set up clear lines of communication via email and through regular face-to-face meetings or teleconferencing, particularly if PGD is carried out in a transport or satellite setting. All such communications should be traceable.

## Document control (ISO 15189: 4.3) and quality and technical records (ISO 15189: 4.13)

There is a considerable amount of documentation required to fulfil the standards, which can be paper-based, electronic or both. Some may argue that providing a clinical service does not require extensive documentation; however, experience shows the value in maintaining robust services, training, traceability, complaint handling and continuous improvement. One way of thinking about the difference between laboratories working within a documentation system compared with laboratories without one is the difference between a symphony orchestra and a jazz band. Both may produce good music but a symphony orchestra respects a musical score (the standards) and is guided by a conductor (the documentation system).

The quality manual should be at the core of the PGD laboratory organization. An effective quality manual describes briefly how the requirements for the standard are met and acts as an index to procedures; it should ideally be no longer than 20–30 pages. The quality manual includes information about the entire organization and responsibilities of the structure to be accredited—the QMS, quality policy, personnel, accommodation and environmental conditions, equipment, information systems and reagents, the examination process (including pre- and post-examination phases) and different ways of monitoring and assuring the quality of testing. Written documentation needs to be produced to support every area of work. There are different types of documents that need to be written (Table III).

Putting in place the documentation is a considerable task and must be carefully prepared. We strongly recommend visiting one or two accredited labs at the beginning of the process of developing the QMS and documentation system, to benefit from their experience and, hopefully, to avoid repeating some of their mistakes. Simply, there are two fundamental requirements:

(1) the documentation must be usable;
(2) it must fulfil the requirements of the chosen accreditation standard.

A good place to start with the documentation is to write the standard operating procedures for the individual tests that the laboratory carries out, taking into account the formal requirements of the standards (ISO 15189, section 5.5.3). Laboratory staff should be involved from the start and understand these processes clearly, as the tests represent the backbone of the service. All the other documentation naturally arises from the examination tests.

The secrets to successful documentation are: ‘write what you do, do what you write’ and ‘write everything—but just once’. A hierarchical approach to documentation should be used, allowing individual documents to be revised without the need to also revise management procedures. One of the keys to successful accreditation is to cross-reference documents to each other. If one document is updated, it does not mean that all the other documents need to be updated as the other documents should refer to the master documents.

By answering a series of questions related to each test, documentation required for the fulfilment of the standards can be logically put into place. For example:

- What is the aim of the test?
- What equipment is required?
- Has the equipment been appropriately installed, calibrated and maintained?
- How was the test validated?
- What are the limitations of the test?
- What internal quality control is required?

**Table III Key types of documents.**

| | |
|---|---|
| Policies | They provide statements that the laboratory will follow particular courses of action (e.g. 101.POL); commonly found in the Quality Manual |
| Procedures | They provide instructions on how to enact policies and how to perform the different activities of the lab. These are also known as standard operating procedures (SOPs). They may be divided into Management Procedures (e.g. 111.MP) and Laboratory Procedures (222.SOP). It may be useful to provide briefer working instructions or ‘Short Procedures’ (e.g. 333.SP), which can, for example, be conveniently used at the lab bench. SOPs are required for all laboratory protocols, equipment and processes |
| Forms | These are used to ensure traceability of all relevant actions and results. Management Forms (444.MF) include training logs, induction records, personnel forms (induction, training and competency logs, health and safety etc.), outcomes of internal audits and minutes of meetings. Laboratory Forms (555.LF) will include request forms, work sheets and results, reagent batch numbers and results of equipment checks and maintenance. Forms can be electronic or hand-filled, but should always be designed to be as simple to use as possible |
| External documents | These are relevant to the QMS or the operation of the laboratory, but are not under the lab’s control (e.g. 123.EXT). They may include laws, regulations, health and safety requirements, guidelines and manuals, as well as documents of other labs and centres: for example, patient information leaflets and consent forms may be external documents under the control of the IVF unit, even if they are written by or with the PGD team |

It is recommended that document/filenames reflect the function of the document; possible abbreviations are suggested.

- What external quality assessment (EQA) is performed?
- Who is trained to carry out the test and use the required equipment?
- How are specimens logged in the lab in order to carry out the test?
- How are test results reported, authorized and filed?
- What are the health and safety risks and requirements?

All of these elements should be addressed, but can be documented according to individual laboratory preference. For example, internal quality control tends to be test-specific and so may be better documented in each test's SOP; whereas equipment is commonly shared between many tests, and so would be more efficiently described in a separate SOP for the individual type of equipment (e.g. use of the fluorescence microscope).

From the outset, careful thought must be given to 'document control' (i.e. the way to ensure that personnel only use approved, up-to-date documents—ISO 15189, section 4.3). A policy document describing the measures taken to prepare, approve, distribute, access, store, change and withdraw documents is essential. In particular, care must be taken when copies exist to ensure that only current versions are in circulation, e.g. by permitting only a set number of printed copies (preferably dated), stored in specified locations. When the document is updated, all previous hardcopy versions of the document are destroyed and replaced with the new edition. If no digital archive is available, one printed copy—clearly labelled as 'expired'—should be kept for as long as required by your accrediting body (or other regulations). All documents of the QMS should contain a header which states the name of the centre, document name, the unique document reference number (including version number or date of issue) and pagination expressed as the page number/total number of pages. Controlled documents need to be clearly identified, such as printing on coloured paper or with a specified coloured header to protect against photocopying. They should, where relevant, contain information on the people authorizing and responsible for the document, the document author, the total number of copies of the document and their locations, as well as an index, a short introduction or scope and cross-references to other relevant documents. All this information can be printed on the document or stored elsewhere in the control system. The QMS and its documentation can be managed in any way the laboratory desires; electronically, on paper, or most commonly as a combination of the two. Dedicated commercial software exists to support quality management; further details are available in a Guidance Report (EuroGentest, 2009).

A 'document index' or 'master sheet' can be prepared to list the documents of the QMS and cross-reference them to the sections of the standard. It may also be convenient to reference external documents such as laws, policies or recommendations relevant to the PGD laboratory in this document.

The laboratory must also have a policy that defines the length of time that documents and records must be retained (ISO 15189, section 4.13). Note that the retention of clinical data is often regulated by national law and/or within hospitals; such regulations must be respected by the QMS. A useful rule of thumb is to equal or exceed retention times defined in local or national regulations.

All documents of the QMS must be periodically 'reviewed' and revised when necessary (see ISO 15189 section 4.12). The quality manager is responsible for maintaining the quality manual and for ensuring that all personnel are aware of the contents of the manual and that the policies and procedures are respected. The frequency is not defined in the standard, with the exception of examination (test) procedures: '5.5.2 Such a review is normally carried out annually'. It should be noted that 'review' does not necessarily imply 'revision'—if no changes are necessary, it is sufficient to state in a document review history that the review was performed and the documents were satisfactory.

The PGD centre needs to establish and implement procedures for the identification, collection, indexing, access, storage, maintenance and safe disposal of quality and technical records. This information can be included in the policies on document control. The PGD centre needs to define the length of time such data is stored. This will relate to request forms, reports, instrument printouts, lab work books, complaints, staff training etc.

## Review of contracts (ISO 15189: 4.4)

It is essential that there is a contract or third-party agreement between the PGD centre and the IVF unit(s), even if they are part of the same organization. This document must clearly state what is expected from the PGD team, the scope of services offered and methods to be used and confirm that the PGD centre is capable of meeting the requirements with appropriate resources and staff and that there will be regular reviews and records of relevant discussions. This document may incorporate, or be complemented by, more detailed Terms and Conditions (outlining such issues as expected test volumes, costs, turnaround times, sample rejection criteria, laboratory working hours etc.).

## Examination by referral laboratories (ISO 15189: 4.5)

This concerns tests and services which are referred to external laboratories. This may include genetics laboratories that perform familial mutation testing or karyotyping as preparation for PGD, when a test is not available in-house or when a second opinion may be required. A procedure must be developed for the choice of competent partners, and the laboratory must follow up and keep records of all referrals.

## External services and supplies (ISO 15189: 4.6)

There must be a procedure for the selection and use of external services, equipment and consumables (see section B3). It is important to identify 'critical reagents, supplies and services that affect the quality of examinations'; these and their suppliers must be followed more closely and must also be verified before clinical use (either experimentally or by using the manufacturer's documentation). For example, PCR tubes or micropipette tips may be considered critical, whereas agarose for analytical gels is not.

One requirement of this section commonly causes concern in laboratories and so is critical to implement efficiently: the requirement to trace lot numbers (section 4.6.3). The optimal solution to this requirement depends on the size and organization of the laboratory and communication with or a visit to an accredited lab may be helpful to see solutions in action.

## Advisory services (ISO 15189: 4.7)

For PGD laboratories, this concerns principally the interactions with the IVF clinicians, who may need advice and guidance in preparing for testing or in future planning. There is an overlap with the contribution to patient care mentioned in ISO 15189 section 4.12.4.

## Resolution of complaints (ISO 15189: 4.8)

Peter Drucker (1909–2005), one of the pioneers of modern management, stated that 'Quality in a service or product is not what you put into it; it is what the customer gets out of it'. ISO 15189 reflects this by the requirement for the laboratory to develop a system to record and resolve feedback from clinicians, patients or other parties. Although it is a formal requirement to record and resolve complaints, it is recommended to extend the system to include positive feedback and requests for information. Such information provides a valuable quality indicator and can contribute to continual improvement. If, for example, there are many identical telephone requests ('what is your fax number?'), it is clear that the lab is not providing the information appropriately to its users.

The simpler the registration system, the higher the chance is of regular usage by personnel and, in turn, of obtaining a comprehensive overview. Figure 1 shows an example form, in use for many years in an accredited molecular genetics laboratory; copies are kept next to all telephones, and the form is widely used and easily analysed.

Centres should regularly review user satisfaction with their services by actively seeking feedback, although this is not a formal requirement of ISO 15189 (section 4.8). In the case of PGD, this concerns principally the IVF unit(s) with whom they work, but—according to the organization—may also include other medical professionals and patients.

For local IVF centres, this can be achieved through regular meetings; an agenda should be circulated to all staff, both teams should have free access to add important issues to the agenda and minutes must be taken and followed up at the start of each meeting. Meetings may not be practical for other users, notably in the case of transport PGD; in such cases, a questionnaire-based user-satisfaction survey can be used. User satisfaction is an important element of the management review (see ISO 15189 section 4.15).

## Non-conformities, corrective actions and preventive actions (ISO 15189: 4.9–4.11)

These elements can be confusing to newcomers to quality management; however, when successfully implemented, they provide some of the major benefits to the laboratory.

'Non-conformity' (also known as non-compliance) exists when any aspect of the laboratory's activity is identified as not conforming with its own procedures or with the agreed requirements of the requesting clinician or the QMS. The laboratory is required to react to the non-conformity. This typically initially involves 'corrective action' to eliminate or reduce the effect of the non-conformity. In the case of 'critical' non-conformities, which may have an impact on patient care, the corrective actions may need to be performed urgently; it may also be necessary to suspend the activity in question, to avoid any risk of recurrence.

Following the immediate corrective actions, the root cause should be identified. If there is a risk of recurrence (which is almost always the case), appropriate 'corrective actions/preventive actions (CAPA)' should be designed and implemented. A follow-up audit should be planned to ensure that the CAPA was effective (that is, had the desired effect) and efficient (effective without an excessive increase in workload).

As with suggestions and complaints (ISO 15189 section 4.8), the initial registration of non-conformities should be simple and accessible to all personnel; the results should be rapidly transmitted to and analysed by appropriate staff. A simple procedure should also exist to encourage the proposal of preventive actions before the detection of non-conformities, for example, by way of a 'suggestions box'.

An important route to and indicator of the successful implementation of a QMS is the clear distinction between 'non-conformity' and 'blame'. The identification of a non-conformity is almost always a sign of a fault in the system, rather than a fault or error by an individual. Personnel should be encouraged to identify and react to non-conformities, but discouraged from denouncing individual people. A 'blame culture' discourages reactions to problems and severely impairs the possibility of quality improvement.

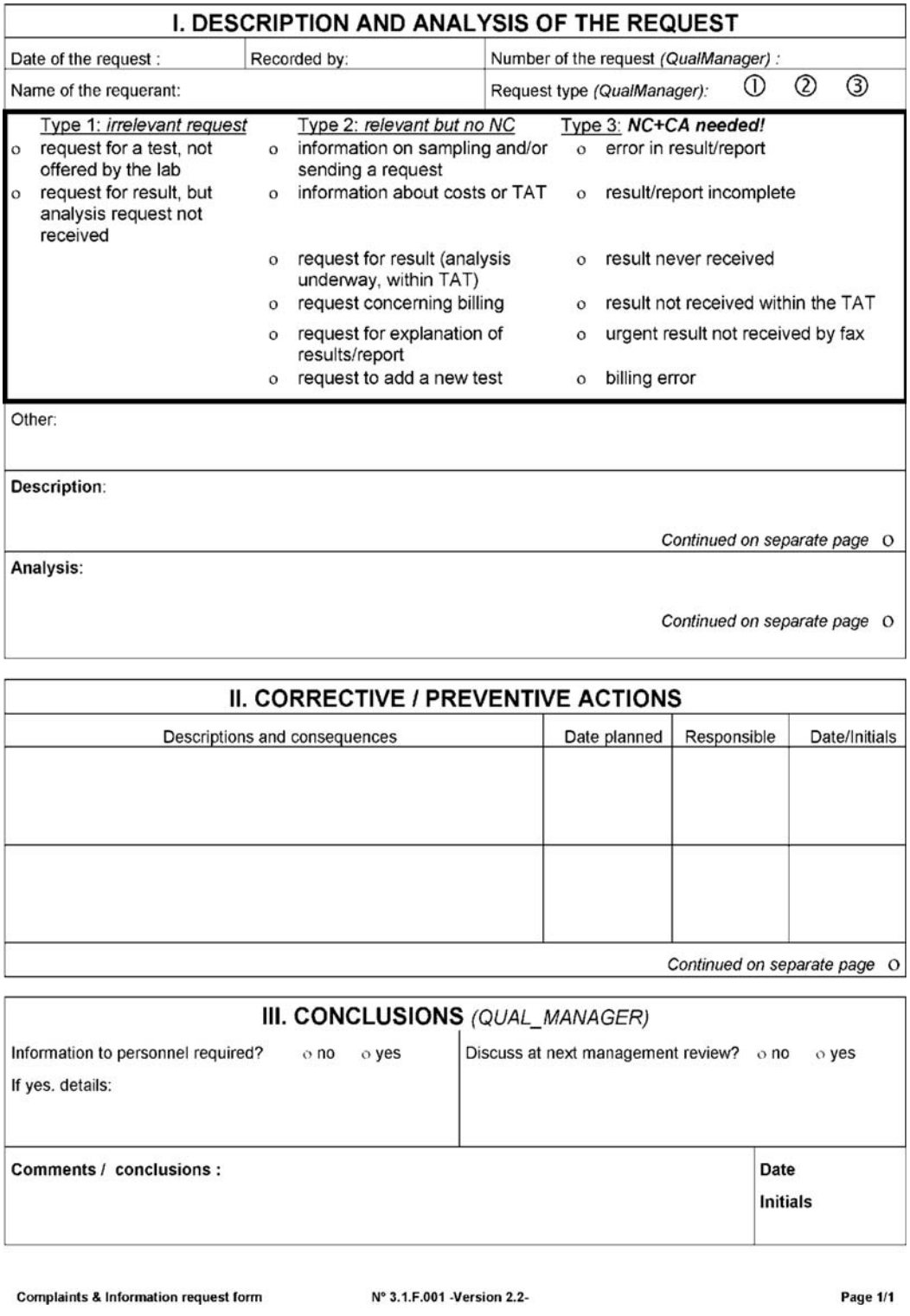
## Continual improvement (ISO 15189: 4.12)

Quality improvement is both a formal requirement and a natural outcome of ISO 15189, based on regular audit and review of procedures, training for personnel and users, CAPA, and any other appropriate mechanism. A successful QMS is dynamic and will evolve to better meet the needs of users (improvement of quality, efficacy) and to reduce the workload on personnel (efficiency). The system must therefore be regularly or continuously evaluated to identify areas for improvement. The quality improvement cycle was famously described by Deming (Fig. 2).

ISO 15189 section 4.12.4 requires that 'Laboratory management shall implement ***quality indicators*** for systematically monitoring and evaluating the laboratory's contribution to patient care'. Quality indicators are a common source of bemusement to newcomers but in fact represent a valuable tool not only in measuring improvement in lab performance, but also in demonstrating these improvements, to staff, users and management alike.

As usual, the standard requires the implementation of quality indicators but does not impose a specific solution or a list: this must be produced by each laboratory according to its activities. Quality indicators should be developed to cover as much of the laboratory's activity as possible, including both technical and management aspects. Quality indicators have to be SMART: specific, measurable, achievable, relevant, time-bound. Therefore, for each quality indicator, it needs to be documented how and how often it is going to be measured, what are the limits and what happens if the limits are not met. For example, the PCR contamination rate is a quality indictor that could be measured every 10 cases with a limit of less than 5%. If this limit is exceeded, the PCR team would need to determine why this limit is being exceeded.

Quality indicators will typically be analysed for and presented at the Annual Management Review (see ISO 15189 section 4.15). Labs are recommended to develop systems for collecting data on an ongoing basis, to ensure a constant overview and to simplify analysis and reporting. Table IV provides examples of quality indicators which can be useful or can be easily adapted to different laboratories.



## I. DESCRIPTION AND ANALYSIS OF THE REQUEST

| Date of the request : | Recorded by: | Number of the request *(QualManager)* : |
|---|---|---|
| Name of the requerant: | | Request type *(QualManager)*: ① ② ③ |

| Type 1: *irrelevant request* | Type 2: *relevant but no NC* | Type 3: ***NC+CA needed!*** |
|---|---|---|
| o request for a test, not offered by the lab | o information on sampling and/or sending a request | o error in result/report |
| o request for result, but analysis request not received | o information about costs or TAT | o result/report incomplete |
| | o request for result (analysis underway, within TAT) | o result never received |
| | o request concerning billing | o result not received within the TAT |
| | o request for explanation of results/report | o urgent result not received by fax |
| | o request to add a new test | o billing error |

Other:

**Description**:

*Continued on separate page* o

**Analysis**:

*Continued on separate page* o

## II. CORRECTIVE / PREVENTIVE ACTIONS

| Descriptions and consequences | Date planned | Responsible | Date/Initials |
|---|---|---|---|
| | | | |
| | | | |

*Continued on separate page* o

## III. CONCLUSIONS *(QUAL_MANAGER)*

| Information to personnel required? o no o yes<br>If yes. details: | Discuss at next management review? o no o yes |
|---|---|

| **Comments / conclusions :** | **Date**<br>**Initials** |
|---|---|

**Complaints & Information request form** **N° 3.1.F.001 -Version 2.2-** **Page 1/1**

**Figure 1** Example of a simple form for noting and following up complaints and requests for information. Note that Type 3 complaints (related to a laboratory error of some sort) require the generation of a non-conformity and corrective actions. NC: non-conformity; CA: corrective action; TAT: turn around times.


**Figure 2** The 'Deming' or 'PDCA' cycle is a rolling circle of four compartments; Plan, Do, Check and Act. Plan, establish objectives and identify the necessary processes to achieve them; Do, implement the new processes; Check, measure and compare the results against the expected outcome; Act, analyse any differences and the level of performance, if necessary, repeat the PDCA cycle.

**Table IV Examples of quality indicators for PGD and molecular genetics laboratories.**

| Technical | Management |
|---|---|
| Number of new tests deployed | Complaints (and compliments) |
| Number of patients/PGD cases tested | Complaint response times |
| Number of tests performed/outsourced | Customer satisfaction survey |
| Positive result rate | Meetings with IVF unit |
| TAT/turnaround time (including from patient DNA reception to preparatory work-up being completed) | Analytical non-conformities |
| External quality assessment results | Outcomes of external audits |
| Internal quality control (IQC) results/score (intermediate precision) | Documents revised and created |
| Test failures | Outcomes of internal audits |
| Number/level of PCR contaminations | Corrective action completion |
| Diagnosis per embryo/single cell | Unplanned absence (including sick leave) |
| Confirmation of results in untransferred embryos | Maintenance of staffing levels |
| Misdiagnosis per untransferred embryo/pregnancy | Maintenance of accreditation |

## Internal audits (ISO 15189: 4.14)

An audit is a systematic, independent and documented process of obtaining evidence and evaluating it objectively to determine the extent to which criteria are fulfilled. Internal audits review and evaluate laboratory activity and the QMS with respect to set criteria, to evaluate the extent to which services meet the needs and requirements of users and comply with the accreditation standard. ISO 15189 requires that particular emphasis be given to areas critically important to patient care. Where indicated, CAPA changes are implemented and further monitoring is used to confirm improvement.

Internal audits are typically conducted by the lab's own staff, although it is theoretically possible to use an external consultant. As personnel should not audit their own activities, it can be beneficial to implement 'crossed audits' between different sections of the laboratory or centre.

For PGD scientists, internal auditing can be one of the most difficult elements of a QMS to implement successfully; it is recommended that at least one member of staff is trained in auditing, either by following an experienced auditor or in a formal training course (see ISO 15189 section 5.1).

Audits can be performed in different ways. 'Horizontal audits' examine a single step in a procedure, across a number of instances, e.g. *CFTR* gene mutation testing for 1 year. 'Vertical audits' inspect the sequential steps of a particular procedure, e.g. a PGD for cystic fibrosis, from receipt of the family samples to completion. 'Examination (or witness) audits' involve observing and questioning an operator performing a particular procedure, to determine understanding of and compliance with the documented protocol (e.g. does the operator perform all critical steps of the procedure in the sequence defined by the SOP). Audits also involve a 'documentary' aspect, checking the policies and procedures in the QMS. In reality, most internal audits are 'mixed', containing elements of all these techniques in varying proportions.

Whichever technique is employed, the main elements of the QMS should be audited every year (ISO 15189 section 4.14.2). To achieve this effectively, the organization must prepare an 'annual audit plan' and implement a policy and procedures on the internal audit process including planning and performing audits, reporting audit results, corrective and preventive action and communication of the audit findings. The precise organization and timing of audits is left to the choice of the laboratory. Performing more frequent audits makes each one quicker and simpler to perform and follow-up, but also means that there are few months without an audit activity. Table V shows an example of an annual plan; many different schedules are possible and each lab must find its preferred solution. Most probably perform 3–7 internal audits per year.

All audits should result in a written report, describing how the evaluated elements of the QMS comply with requirements. A template audit report form should be used. An audit may often necessitate a re-audit so there should be a clear re-audit cycle. One way to do this is to construct a re-audit calendar which clearly lists all the re-audits necessary. A re-audit form should be used to report the re-audit. The reports of all audits should be reported to the laboratory QM meeting.

Audits often generate corrective or preventive actions which in turn should be described and implemented. As stated in ISO 15189 sections 4.9–4.11 earlier, CAPA should be followed up to evaluate their effectiveness and efficiency. The time interval to the follow-up should be intelligently chosen according to the situation: a corrective action that is potentially critical to patient care might need following-up rapidly (even, conceivably, same day), whereas others can be evaluated at the following year's audit.

## Management review (ISO 15189: 4.15)

The PGD centre management must review the QMS and all the medical activity. The review has two major aims:

**Table V Example annual internal audit plan, for ISO 15189.**

| | |
|---|---|
| March | Organization and management, QMS, management review |
| April | Personnel, training and continuous education, competence |
| May | Witness audit of one analytical procedure (including examination procedures, assuring quality of examination procedures, health and safety, accommodation and environment) |
| June | Equipment and instruments, reagents, external services and supplies |
| September | Non-conformities, internal audit, corrective/preventive actions |
| October | Vertical audit: one sample from pre- to post-analytical (including examination procedures, assuring quality of examination procedures, health and safety, accommodation and environment) |
| November | Reporting of results, quality and technical records, advisory services, referral laboratories, document control |
| *January* | *Annual Management Review* |

The annual management review is included in this plan for convenience.

**Table VI Items to be included in the management review.**

| |
|---|
| (a) Follow-up of previous management reviews |
| (b) Status of corrective actions taken and required preventive action |
| (c) Reports from managerial and supervisory personnel |
| (d) The outcome of recent internal audits |
| (e) Assessment by external bodies |
| (f) The outcome of external quality assessment and other forms of interlaboratory comparison |
| (g) Any changes in the volume and type of work undertaken |
| (h) Feedback, including complaints and other relevant factors, from clinicians, patients and other parties |
| (i) Quality indicators for monitoring the laboratory's contribution to patient care |
| (j) Non-conformities |
| (k) Monitoring of turnaround time |
| (l) Results of continuous improvement processes |
| (m) Evaluation of suppliers |
| And additionally for PGD (not listed in the standards) |
| Summary of PGD cases for all the IVF centres (*n*) |

According to ISO 15189, section 4.15.2: 'Management review shall take account of, but not be limited to:'.

- to ensure the suitability and effectiveness of the services and QMS for patient care;
- to identify and introduce any necessary changes or improvements.

The review is typically performed as an annual management review but a shorter interval should be adopted when the QMS is being established.

The required content of the review is detailed in the standard (Table VI). In the context of PGD, it should also include a summary of the PGD cases in the previous period [if the PGD is being performed with multiple users (IVF centres), the total results for all IVF units should be included] and an update on staffing levels. The reports from the managerial and supervisory personnel could include a summary of the activities of the centre, publications, meetings attended, training and education. Reports following a detailed analysis of relevant quality indicators are particularly valuable; examples of suitable indicators are presented in Table V.

Action plans must be developed for decisions and other tangible outcomes of the management review. The results should be communicated appropriately to personnel.

# Technical requirements

## Personnel (ISO 15189: 5.1)

The requirements of ISO 15189 with respect to personnel are based on the principle that there should be sufficient competent personnel to meet the needs of the laboratory and that documentary evidence of this be readily available. The central concept, 'competence', can be generally understood as the product of basic academic, postgraduate and continuing education, as well as training and experience.

The PGD laboratory shall be ***directed*** 'by a person or persons having executive responsibility and the competence to assume responsibility for the services provided' (ISO 15189 section 5.1.3). The precise requirements for such competence are not detailed but are commonly specified elsewhere by the national professional group. In the UK, for example, this is recognized as being a member of the Royal College of Pathologists or equivalent, and only this person can sign-off reports. In addition to the responsibilities of running the PGD laboratory, the director's job description and competence must include the technical and managerial elements specified by the standard (ISO 15189 section 5.1.4).

Note that the phrase 'by a person or persons' implies that responsibilities can be distributed between different individuals. It is simply necessary that each essential task is the responsibility of an identified individual and that appropriate provisions for his/her replacement are made in the case of absence.

The laboratory must also appoint a 'quality manager' (however named) with delegated responsibility and authority to oversee compliance with the requirements of the QMS.

Although it is essential in PGD that the procedures be carried out by suitably qualified personnel (Geraedts *et al.*, 2001; Vendrell *et al.*, 2009), currently no recognized training programmes exist. In some cases, this may lead to inappropriate situations where, for example, the medical director may wish to perform the biopsy and the clinical embryologist the FISH or PCR. All personnel must be fully trained to perform the tasks which they will undertake. Biopsy should be performed by a clinical embryologist who is performing embryology on a regular basis; in most countries, some form of certification exists (e.g. ESHRE have developed a system for certification of clinical embryologists; www.eshre.org). FISH should be performed by a suitably qualified cytogeneticist and PCR by a molecular geneticist. The most important issue is that whoever performs the testing must have appropriate training in single-cell diagnosis (Harton *et al.*, in preparation).

Personnel (laboratory, management and administrative staff) must have defined initial and continuous 'training programmes',

encompassing all areas of work including as appropriate the use of equipment, SOPs, data protection, training in the IVF unit and health and safety.

Personnel must receive 'training in quality assurance' and quality management (ISO 15189 section 5.1.6). This should be adapted appropriately to their tasks; secretaries, cleaning staff, technicians and scientists will have very different needs. As mentioned above, personnel performing internal audits must receive specific training. Such training can be performed in-house by staff with experience in quality management, by visits to other laboratories, or in formal quality management training programmes such as the EuroGentest (2009) Workshops on Accreditation.

In all cases, it is necessary to document that training has been performed and that it was effective: i.e. from a specified date, the person is 'competent' to perform the task. In some situations, formal competency tests will be required, for example, for an apparatus or a test procedure; in other cases, competence can be tested by the trainer based on common sense and observation. It may be appropriate for the formal authorization of competence (required by ISO 15189 section 5.1.7) to be signed by the trainee ('I believe I am competent to do this'), by the trainer ('this person is competent') and by the director who is responsible for the accuracy of the final result.

Training should be given by an appropriate person and records kept in the staff's logbook. All staff need to keep a log of their continuing professional development (CPD) to ensure continual updating of their competency. The laboratory should have a policy for maintaining competence, for example, for tests that are performed very rarely or in the case of prolonged absence of specific personnel.

Although not a formal requirement of ISO 15189, all staff should have an annual appraisal interview, typically with their line manager. Appraisals should take into account what has been achieved since the last appraisal, if there were any obstacles to obtaining these, a summary of training taken and what training needs to be conducted in the following year. This interview thus provides a valuable tool for evaluating the effectiveness of training and for identifying necessary or useful future training, as required by the standard. Staff should be given the form to complete in advance of the appraisal date and this should be returned to the interviewee to access. Formal record should be kept.

Policies and procedures for 'personnel management' should describe how the personnel system is operated, including the professional direction (who directs the centre), an outline of the staffing of the PGD centre (who is employed, in which positions), replacements, recruitment, personnel records (what they are and where they are stored), staff orientation and induction, job descriptions and contracts, staff records, the annual appraisal process, staff training and education and continued professional development. A confidential file should be kept for all staff with copies kept by the laboratory manager and the staff member. This should include job title, job descriptions, contracts, terms and conditions, accountability and responsibility, induction, education and CPD, absence records, accident records, occupational health, disciplinary action, staff meetings and annual reviews.

## Accommodation and environmental conditions (ISO 15189: 5.2)

As is the case with personnel, the accommodation and environment of the PGD laboratory must be 'adequate' for the tasks and the workload, without compromising quality, safety or patient care. The standard does not define precisely the requirements, which are typically considered as a matter of professional judgement. In this respect, the accreditation body may make use of published guidelines (e.g. Thornhill *et al*., 2005).

The procedures for 'accommodation and environment' must include details of the facilities for staff, patients, storage, health and safety. This should include a plan of the PGD centre and a description of the facilities, an outline of the facilities specifically for staff (this should include adequate toilet and rest areas and somewhere to eat and drink) and patients (patients may only be seen at the IVF centre and may not attend the PGD centre, but if they do, the facilities need to be under quality management). Facilities for storage must include details of how samples, consumables, hazardous substances, drugs, reagents and waste materials are stored. The laboratories, offices and storage areas must be well organized and in a good state of repair. As is usual, the standard does not include PGD-specific requirements; these should be specified with a mix of professional judgement and common sense.

PCR facilities provide a good example of how to interpret the standard within a specific domain. Separate pre- and post-PCR facilities are widely regarded as essential in diagnostic facilities, and indeed their absence would almost certainly preclude accreditation of a PGD lab; yet the standard contains no mention at all of pre- or post-PCR facilities. In contrast, section 5.2.6 states that 'There shall be effective separation between adjacent laboratory sections in which there are incompatible activities. Measures shall be taken to prevent cross-contamination'; a technical assessor would certainly interpret this as a formal requirement to separate the two activities.

The formal requirements of the standard concerning ***health and safety*** are not very detailed, requiring principally training to avoid adverse incidents, appropriate environment and safe usage of equipment. While it is probable that the majority of health and safety policy and procedures will be defined by applicable legislation, which takes precedence over accreditation requirements, the laboratory should consider defining and documenting its health and safety procedures at the same time as preparing for accreditation. Because of the impossibility of controlling egg collection dates, which is dependent on the patients' response to stimulation, many PGD centres will perform diagnosis seven days a week. The health and safety procedures should address 'out-of-hours' practices, including lines of communication, authorization for working alone and/or out-of-hours and professional responsibility, in accordance with applicable legislation.

Procedures should document 'good laboratory practice', e.g. the use of personnel protective equipment, safe working in the laboratory including protective equipment (such as laboratory coats, wearing gloves, safety glasses), safe use of equipment, chemicals and reagents and general laboratory housekeeping such as cleaning and end-of-day and end-of-week procedures. It can be useful to have existing and new staff sign safety procedures, for traceability.

This section also addresses control of access. The 'rules for access' by personnel, visitors and patients should be clearly defined and a log of visits should be kept. It is common practice to require visitors to sign in and out in a log book which contains a brief summary of the conditions for visitors and a pledge to respect professional confidentiality.

## Laboratory equipment (ISO 15189: 5.3)

Note that the term 'equipment' specifically includes not only apparatus and instruments, but also all consumables, reagents, reference materials and also computer software used in examination procedures.

The simple requirement is once again that the laboratory is equipped with all items required for provision of its services. The text of 5.3.2 is central: 'Equipment shall be shown (upon installation and in routine use) to be capable of achieving the performance required and shall comply with specifications relevant to the examinations concerned'. On due consideration, it is evident that meeting these requirements requires intelligent planning, organization and effort.

- First, the 'performance specifications' must be defined, for each examination and for all associated equipment.
- Equipment must be selected that will comply with these specifications.
- Before use in testing, equipment must be 'shown to be compliant' by the laboratory; this is clearly related to validation and verification, also addressed in ISO 15189 section 5.5.
- The laboratory must also be able to show that equipment meets requirements on a continuous basis: this implies appropriate use of internal quality control, calibration and maintenance.
- In the case of 'repair', it must again be shown that the equipment is compliant.
- The laboratory must have appropriate procedures in the case of 'failure' of critical equipment (e.g. back-up equipment, service contracts, timely repair or replacement or outsourcing of examinations). Note that, in the PGD laboratory, failure of critical equipment is arguably more significant than in many routine testing laboratories as a result of the rapid turnaround times and inability to retest many single-cell samples.

New equipment should be purchased according to standardized, documented procedures; the performance criteria for the intended application should be documented. All equipment must be uniquely identified, and the laboratory must maintain a complete inventory of equipment. It is useful for laboratory management to designate a reference person for each item (or class) of equipment, including information technology, to oversee the instrument and as a contact in the case of malfunctioning or other related issues.

Complete equipment records must be maintained. Instructions for use must be readily available in a language readily understood by the relevant personnel. One convenient solution uses a folder for each instrument, stored next to the instrument, documenting all the elements listed in ISO 15189 section 5.3.4, as well as a form identifying trained authorized users (this information should also be stored in their training logs) and a history of relevant calibrations and controls, failures, performance checks and repairs.

Monitoring of equipment can be performed manually or automatically and intermittently or continuously. The required monitoring must be defined for each individual item of equipment, but should be proportional. A liquid nitrogen container or an incubator for embryo culture requires continuous monitoring and an out-of-temperature alarm, but this may be excessive (and excessively costly) for a refrigerator for storage of routine reagents: it may be sufficient simply to record the temperature manually once per week, e.g. before opening on Monday morning. Acceptable temperature ranges must be defined for all incubators and 'cold-chain' equipment. The acceptable duration of out-of-range events should also be considered, to avoid excessive alarms every time a freezer is opened; it is common practice to keep temperature probes in a tube of 50% glycerol if brief changes in temperature are not significant. Zonal changes within equipment should also be considered (top–bottom and front–back).

For some critical instruments, it can be useful to have a brief SOP with emergency procedures on the instrument. For example, an incubator could indicate a procedure for and out-of-temperature failure, such as

'If above 38.5°C:

(1) move cultures to back-up incubator no. 123;
(2) contact maintenance on telephone 456789;
(3) contact scientist Dr X;
(4) document on form A1'

Computer software and systems must be addressed in the same way as instruments: their compliance to requirements must be shown, instructions must be available, and training and authorization is necessary before use. Patient confidentiality must be respected, on primary systems and on back-ups. Competence records must indicate which staff is authorized to use information systems and/or to enter data. The documented instructions on usage, validation and maintenance should also consider the issue of data back-up and software upgrades. If software is upgraded, it will probably be necessary to revaluate its compliance in some way. When critical programmes are installed on personal computers, it is often appropriate to disable automatic updates of the operating system, which can potentially lead to incompatibilities.

In general, it is not necessary to validate and document equipment that is non-technical and non-critical, e.g. a photocopier or a word-processor. Common sense and professional judgement must be used to determine whether performance is critical for the examination procedures: a camera that is simply used to photograph a mini-gel may not need consideration, but one that is used to capture FISH images (the interpretation of which directly affect patient care) will need validation, control and routine preventative maintenance and periodic servicing.

The issue of the cohabitation of diagnostic testing and research activities, with shared use of space, instruments and reagents, must be considered. There is no formal barrier in the standard to this, but it adds two constraints. Firstly, it is necessary to be entirely clear what activity is included within the accreditation scope; typically, only diagnostic testing would be included although research and development, leading to new diagnostic tests, may also be included. Secondly, it is appropriate that all personnel should work according to the rules of the accredited activity. Initially this can lead to resistance from research personnel; but the benefits of working under more controlled and reliable conditions often provide a convincing argument. It is important to note that the validation of tests, which can be at the routine/research interface, must be performed on production equipment, and therefore within the accredited environment.

Documentation should address all aspects of equipment acquisition and use. Purchase of equipment should follow standard protocols comprising product criteria, manufacturing criteria, and risk and

safety evaluation. All received goods should be controlled, identified, registered and released according to SOPs. Home-made reagents should meet described quality criteria and records be available for auditing. Composition, concentration and date of fabrication and/or expiry date must be clearly identified; as expiry dates must be respected, it is recommended to indicate them on reagents wherever possible. Stock should be managed; in particular, supplies of critical reagents must be assured. Hazardous reagents should be registered, labelled, stored, managed and used appropriately, waste disposal (chemical, infectious, hazardous) must be described, although the details typically depend on local legislation rather than the standard. All consumables used for clinical work must be logged in and a record taken of certificate of analysis, batch number, reception date, starting date of use, expiry date, conditions and place of storage, and necessary validation.

The ESHRE Best Practice Guidelines (Thornhill *et al*., 2005) contain PGD-specific recommendations concerning equipment and reagents; although these are not formal requirements for accreditation, they are of value to the laboratory and are expert guidelines which may be considered by assessors. As such, it is recommended to incorporate them into the QMS.

## Pre-examination procedures (ISO 15189: 5.4)

*Validation of specific PGD protocols (PGD workup)*

A peculiarity of many PGD protocols is that the clinical test used is frequently developed for a specific couple. For example, the design and use of specific probe combinations for patients carrying reciprocal translocations and the use of informative markers for couples at risk of transmitting a specific single-gene disorder. All such customized protocols must be validated before clinical use. The report must define the couple for whom the test has been validated, the exact protocol validated and how it was validated (number of single-cells analysed etc.). This report should be authorized in the same way as any other report (see ISO 15189 section 5.7). IQC should be in place for each validated protocol so that just before the clinical PGD cycle, reagents and equipment are checked to ensure that the IQC meets the standards set.

ISO 15189 sections 5.4–5.7 address the technical procedures that have the greatest impact on patient safety. They are designed to assure that the correct patient receives an accurate result for the correct test, within an appropriate time. These sections of the standard are very clear and precise and are easily applicable, even for laboratories with little direct experience of quality management. Most laboratories will already have thorough systems in place for the aspects addressed by the standard; given the extreme importance, and the immediate benefit to patient care, it is recommended that laboratories focus on the detailed requirements of the standard in this respect early in the development of their QMS.

Documentation for this section must fulfil two groups of requirements: the 'procedures for the PGD laboratory' itself, and the 'primary sample collection manual' for users. PGD labs have specific pre-analytical constraints compared with other genetics laboratories, because such a large proportion of samples are irreplaceable and require urgent testing. In a molecular or cytogenetics laboratory samples will be mostly blood for DNA preparation or for leukocyte culture. The PGD laboratory will often receive not only such conventional samples (for confirmation of familial anomalies), but also biopsied cells (polar bodies, blastomeres or trophectoderm) and possibly whole embryos or single embryonic cells (for confirmation of the biopsy result). When dealing with single-cell samples, there is very little margin for error when collecting, receiving and processing a sample for testing: poor handling of single cells for either PCR or FISH analysis will probably lead to test failure, contamination or both.

The sample collection manual must include information for users (IVF units, geneticists or others) and patients, test ordering and patient referral, specimen collection, handling and processing, transportation, reception, storage and eventual referral to other labs. A more formal contract between IVF centre and PGD lab, including the detailed Terms and Conditions, may be appropriate. Clear and comprehensive information for patients is important to assist informed consent and to help provide realistic expectations regarding the likelihood of success. This is particularly important for PGD, in which (i) diseases with different modes of inheritance lead to different chances of success following PGD, (ii) the sensitivity of the techniques used combined with the single-cell biopsy make test failure more common than with routine diagnostic testing. The exact content of written patient's information materials will be specific to the disease type and strategy used for diagnosis, but the practical steps involved in PGD, test accuracy and reliability, misdiagnosis rate and likely success rates are all essential items of information required for patients, as stated previously in professional guidelines and recommendations (PGDIS, 2004; Thornhill *et al*., 2005) and, in some cases, regulatory bodies (HFEA, 2009).

Specimen collection raises specific challenges for PGD since at present, the biopsy and preparation of single blastomeres, polar bodies or multiple cells from blastocyst biopsies is only conducted by a relatively small number of practitioners worldwide. Furthermore, the labelling and the number of cells to be removed at biopsy are critical. The laboratory should prepare very detailed SOPs describing single cell preparation methods; it may also be appropriate to consider offering training to the IVF clinics commissioning diagnostic tests.

The PGD laboratory should validate the sample transportation protocols from the commissioning IVF clinic to ensure that (i) specimens are not lost or delayed, (ii) transport of cells does not compromise the efficiency of PCR amplification or FISH hybridization and (iii) any prearranged turnaround times from sample preparation to result reporting can be met. Such validation is usually performed by a series of tests involving: repeated transportation of non-critical materials, dummy-runs and simulated cycles.

The standard insists on proper identification of primary samples (ISO 15189 section 5.4.5) and states unequivocally 'Primary samples lacking proper identification shall not be accepted or processed by the laboratory'. However, it also admits the possibility of accepting critical samples (such as biopsied cells) that are inadequately labelled under certain conditions. There is commonly pressure on the laboratory to accept samples despite insufficient identification; as it is critical for the laboratory to avoid giving a result for the wrong sample, it is recommended that a precise and comprehensive procedure be developed for the treatment of such situations, including the basic policy of 'rejecting inadequately identified samples'**.** Rapid and frank communication with the referring clinician should be included in the procedure to attempt to resolve the immediate problem and also to reduce the risk of recurrence. The collection manual and/or request form should also indicate clearly what the laboratory requires as identification.

Once the samples arrive in the PGD laboratory, they should be logged in as for any other clinical sample. The single-cell sensitivity

and limited ability to re-test samples collected for PGD make it critical to ensure that the correct test is ordered for the patient, after appropriate pre-test counselling and test development (if appropriate). A written confirmation of the specific test to be performed should be received by the diagnostic laboratory, preferably in advance of specimen receipt; this is best achieved using a requisition form provided by the diagnostic laboratory. Specimens arriving without such documentation should, in principle, be rejected, with the same potential exceptions as described for unlabelled or incorrectly labelled samples. The standard also requires that requests and samples be systematically 'reviewed by authorized personnel' (ISO 15189 section 5.4.10); this must be documented, for example, by initials and date on the request form. Non-conformities at reception should be treated in a timely manner, proportionate to the degree of urgency; particularly in the PGD lab. This may require specific training for the personnel involved to ensure they are sensitive to sample storage requirements, additives and urgency.

## Examination (test) procedures (ISO 15189: 5.5)

There should be a written procedure for the conduct of all examinations and moreover that the adherence to examination procedures is essential to ensure a consistent and reliable quality service. For the 'examination procedure', this includes the selection and validation of the examination procedure, and assuring the quality of the examination.

Only validated protocols should be used for clinical PGD (see ISO 15189 section 5.4). Critical steps in the diagnosis will need to be appropriately witnessed. Since some tests are individual protocols for specific couples, it may be useful to prepare a protocol summary table where the person performing the diagnosis and the witness can record exactly what they did for each critical stage of the protocol (and both sign that they did it/witnessed it), e.g. for a FISH case, the identity and volume of probes used and the denaturation and hybridization times. Competence records should be kept indicating which personnel are authorized to perform particular procedures.

The laboratory director shall be responsible for ensuring that the content of examination procedures are complete, current and have been thoroughly reviewed. The same requirements for document control should also apply to electronic manuals.

There needs to be a policy on the control of 'process and quality records'**.** In this document, there is information on the types of laboratory forms (and their reference numbers), how these forms are stored and where they are stored for easy retrieval. Individual staff should not store this information in personal laboratory books. This information must be readily available and accessible to those with documented access. It is also important to know what documentation needs to come with samples from IVF laboratories (PGD referral forms). Ideally, basic information should be obtained from the IVF unit regarding the IVF cycle, such as the number of eggs collected, number fertilized, method of biopsy etc. In some cases (e.g. full members of the ESHRE PGD Consortium), this is essential. Such information may be considered as good practice, especially for those centres operating transport PGD. The policy should also contain information on how the results of the PGD workups and cycle results are stored (such as gels, FISH images etc.). This MP also needs to contain information on patient consent but this would normally come under the control of the IVF unit. Lastly, the document needs to contain information on where the quality records are stored (audit reports, EQA results, annual management reviews and user satisfaction reports).

## Assuring quality of examination procedures (ISO 15189: 5.6)

Validation and IQC of the protocol before the clinical case (see ISO 15189 section 5.4), and monitoring of the quality indicators for cases (see ISO 15189 section 4.12), will ensure that the quality of examination procedures is continuously monitored.

### *External quality assessment*

A policy on EQA needs to include details of the EQA that the PGD laboratory uses, who in the PGD centre is responsible for doing the EQA (processing the samples etc.) and how the EQA is reported. An accreditation system cannot operate unless there is an EQA or equivalent which can monitor performance. The PGD Consortium has set up schemes for EQA of FISH in collaboration with CEQA (Cytogenetics European Quality Assessment, www.ceqa-cyto.eu) and PCR in collaboration with UK NEQAS (UK National External Quality Assessment Scheme, http://www.ukneqas.org.uk).

Laboratories should also consider participation in genetics EQA schemes which are not PGD-specific, especially when parental and/or familial testing is performed. When no EQA scheme is available for a particular disease or type of analysis, the laboratory should consider sample exchange with another laboratory to demonstrate the accuracy of testing.

## Post-examination procedures and reporting of results (ISO 15189: 5.7)

The post-examination procedure could be defined as 'processes following the examination, including systematic review, formatting and

**Table VII Items that should be included in the PGD cycle report which is sent to the IVF unit.**

| |
|---|
| Name (and address) of the PGD unit |
| Name (and address) of the IVF unit |
| Name and number of the report form (as used for document control) |
| Date of the egg collection |
| Date of the report |
| Unique patient number |
| Unique cycle identifying number |
| A summary of the results—ideally in tabulated form |
| Interpretative comments—which embryos should be considered for transfer |
| (Highlighting of abnormal results) |
| Identification of the person performing the diagnosis and the witness |
| Identification of the person verifying the results and authorizing the release of the report and their signature |
| Pagination to include the actual and total number of pages |

**Table VIII** Report form 1-PGD INTERNAL REPORT.

**Report of Preimplantation Genetic Diagnosis**

Name and address of PGD Centre

Name and address of IVF unit

*This form needs two unique patient identifiers, e.g. name and dob. It also needs a laboratory ID reference which is unique to that couple and cycle, e.g. the patient's hospital number and PGD cycle number*
Patient number:
Lab ID (unique identifier):
Date of egg collection or date of biopsy:
Time and date sample received in PGD lab:
Time and date report issued:

*Maternal and paternal details need to be filled in as appropriate using full ISCN 2009 for abnormal karyotype or disorder (OMIM number), gene (OMIM number), accession number of reference sequence (plus version number), Mutation(s) using Human Genome Variation Society (HGVS) nomenclature*

Maternal name:
Maternal dob:
Maternal karyotype or mutation

Paternal name:
Paternal dob:
Paternal karyotype or mutation:

Brief details of protocol used as such FISH probes, *markers used, genetic distance of markers used in testing, parental haplotypes, error rates clearly stated* etc.

Person performing Diagnosis: (Name and signature)
Witness/checker: (Name and signature)

Report

| Embryo code | Details of analysis | Overall result | Transferable yes or no |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

Signed: Head of laboratory: (Name, signature and date)

interpretation, authorization for release, reporting and transmission of result and storage of the samples of the examinations' CPA (2007).

The policy for the post-examination phase needs to include details of who reports the results and on what forms, the confidentiality of the reports, the internal (detailed laboratory report of the PGD case) and the external report (the summary report for the IVF unit), how the reports are authorized and by whom and how the results are reported. Results shall be legible, without mistakes and reported to persons authorized to receive and use this kind of medical information.

The laboratory shall have clearly documented procedures for releasing of examination results, including designated personnel responsible for releasing the results and to whom they can be released. It is recommended not to release the information on the embryos to be transferred verbally (by phone) to prevent a misunderstanding which could result in the transfer of the wrong embryo. Therefore only emailed, faxed or hardcopy reports should be used in PGD. Only the latter two can contain an authorizing signature unless using an approved electronic signature in scanned reports by email. For PGD, it may be useful to email a provisional report so that the embryologists can score the embryos to determine their development since the biopsy. This will be useful information when discussing the results with the patients (if customary) and deciding which embryos to replace. However, a hardcopy report signed by the authorizing personnel is needed by the IVF unit before embryo transfer is conducted. If this is faxed, provisions need to be in place to ensure that it is faxed to the correct location (receipt confirmation) and that the fax machine is secure (i.e. in a controlled location). It is a good practice for the PGD team to be available to discuss the report with the IVF team.

**Table IX** Report form 2-Report to be sent to the IVF unit.

**Report of Preimplantation Genetic Diagnosis**

Name and address of PGD Centre

Name and address of IVF unit

Patient number:
Lab ID (unique identifier):
Date of egg collection or date of biopsy:
Time and date sample received in PGD lab:
Time and date report issued:

Maternal name:
Maternal dob:
Maternal karyotype or disorder/mutation:

Paternal name:
Paternal dob:
Paternal karyotype or disorder/mutation:

Person performing Diagnosis: (Name and signature)
Witness/checker: (Name and signature)

**Summary of results:**
The results of the biopsy and FISH/PCR from blastomeres (or polar bodies) from embryos xx, xx, xx and xx showed a normal pattern and so these embryos may be considered for transfer *(complete as appropriate)*

**Report**

| Embryo code | Overall result | Transferable *yes or no* |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

Signed by PGD lab head: (Name and signature)

Information on which embryos were transferred, any resulting pregnancy and delivery need to be reported to the PGD laboratory.

*PGD is based on X cells removed from each embryo. The accuracy of the result is estimated to be XX. The accuracy of the results is based on the assumption that :- samples received were correctly identified, family relationships are true and clinical diagnosis of relatives is correct.*

The following items should be part of the PGD report (Table VII) and examples of report forms for PGD are shown in Tables VIII and IX.

## Conclusion

Regulations or recommendations in many countries are already requiring that any diagnostic laboratory should be accredited (OECD, 2007; HFEA, 2009) and the ESHRE PGD Consortium recommends that all PGD centres should be preparing for accreditation (Goossens *et al.*, 2009). The implementation of a comprehensive QMS and the preparation for accreditation is initially a daunting experience, and in this document, we have addressed specific issues relating to PGD, to make this process easier and to provide a degree of harmonization between laboratories. Accreditation is a time-consuming process both in the initial and in the maintenance phases. However, the value of a comprehensive QMS rapidly becomes clear to any PGD centre, along with the realization that many areas were potentially vulnerable. A good starting point is to involve the whole PGD team in the QMS, especially in writing SOPs for the different laboratory procedures and to put in place appropriate instructions and documentation for laboratory instruments. This can be followed by ensuring all the personnel information is in place (including the training manual), after which the quality manual and the detailed policies can follow.

PGD is a multidisciplinary procedure that requires excellent organization and communication. To date, there are no nationally or

internationally recognized training programmes for PGD (as exist in other fields of diagnosis, such as cytogenetics and molecular genetics). For this reason, development of a well-defined internal training programme, maintenance of log books and CPD for all personnel involved in PGD is essential. Maintaining a quality system is an active process that requires everyone on board, requiring continuous education and motivation of all personnel. A well-maintained QMS will standardize the PGD service, prevent reliance on individuals and generate a more reliable service ultimately leading to improved patient care as measured by increased effectiveness for both the IVF and PGD centres involved (Vendrell *et al*., 2009).

The ESHRE PGD Consortium has organized two workshops to address the issues relating to accrediting a PGD centre (www.eshre.com). In addition, four new guidelines on PGD are in preparation. They will be on: organization of the PGD centre, FISH, PCR and embryo biopsy/embryology (Harton *et al*., in preparation). This paper should be read in conjunction with the new guidelines for anyone working in the field of PGD.

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*Submitted on October 19, 2009; resubmitted on November 20, 2009; accepted on November 30, 2009*