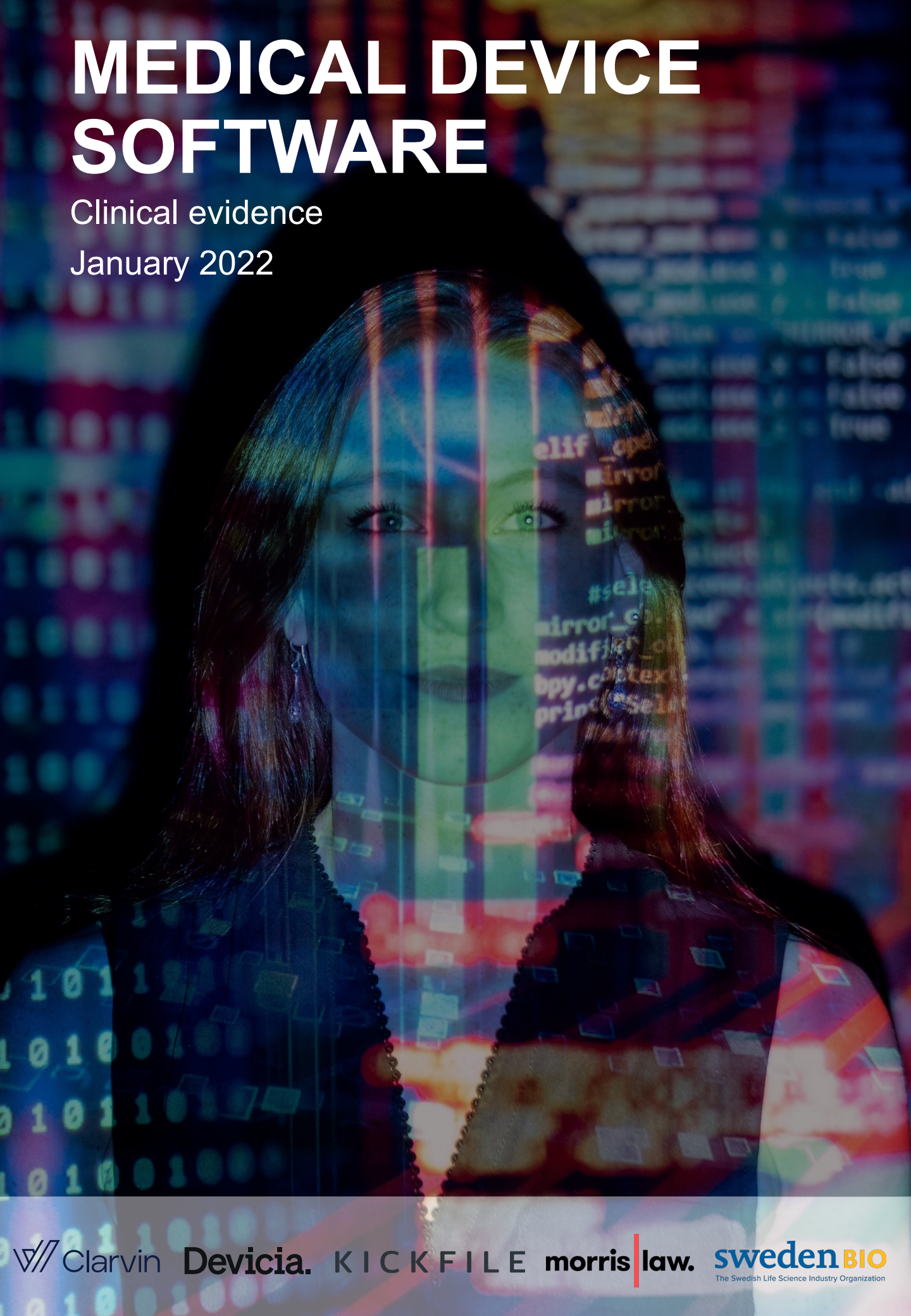
MEDICAL DEVICE SOFTWARE

Clinical evidence

January 2022



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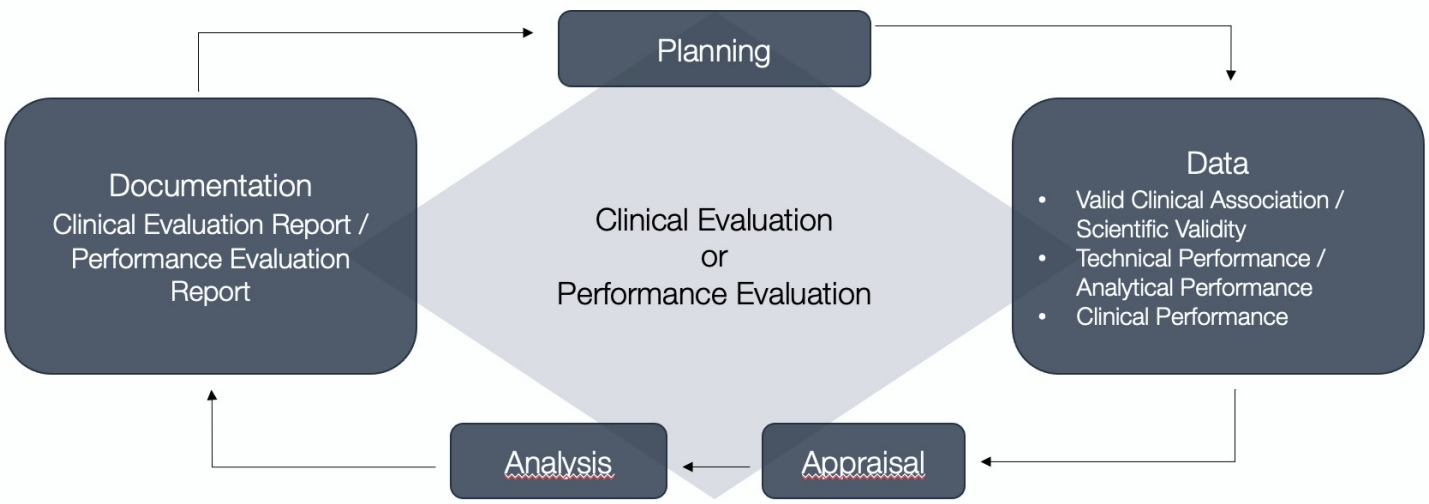
INTRODUCTION

A clinical evaluation/performance evaluation is required for CE marking of a medical device/*in vitro* diagnostic medical device.[1] The purpose of such an evaluation is to provide sufficient clinical evidence to demonstrate conformity with the applicable general safety and performance requirements ("GSPRs") under normal conditions of the device's intended purpose. The evaluation requirement also applies to medical device software ("MDSW"). The unique characteristics of MDSW – such as the lack of contact with the human body – means that although clinical/performance evaluation of MDSW is based on the same regulatory requirements as other types of medical devices, there are special considerations to bear in mind when determining the type and amount of data needed to support the intended purpose and clinical claims. This is why the EU Medical Device Coordination Group ("MDCG") has issued guidance specifically for clinical/performance evaluation of MDSW, **MDCG 2020-1.** This white paper aims to provide an overview of the evaluation process for MDSW – shown schematically below.

Flowchart for clinical/performance evaluation of medical device software (adapted from MDCG 2020-1)



[1] MDSW can be either general medical devices or in vitro diagnostic medical devices ("IVDs"). General medical devices are regulated by the Medical Device Regulation – "MDR" (EU 2017/745) whereas IVDs will be regulated by the In Vitro Diagnostic Regulation – "IVDR" (EU 2017/746) as of 26 May 2022. The terminology related to clinical evaluation varies for the two product types, e.g., the term "clinical evaluation" is used for general devices whereas "performance evaluation" is used for IVDs.

PLANNING: SCOPING AND THE EVALUATION PLAN[2]

The first step of a clinical/performance evaluation is to determine the scope, based on the relevant GSPRs that need to be addressed from a clinical perspective, also considering the intended purpose and clinical benefits. This step constitutes the planning stage of the evaluation during which the evaluation plan shall be prepared. The result of the scoping will help determine the type and amount of data needed to support the evidence goals. The requirements for evaluation plans are clearly described in the MDR and IVDR.

Generally, clinical/performance evaluation shall first be performed during product development to identify the clinical data needed for regulatory purposes, and also assess if product-specific clinical data need to be generated. The progress of the latter shall under the MDR be captured in the Clinical Development Plan ("CDP"), which constitutes an important part of the evaluation plan. The CDP does not only satisfy a regulatory requirement, but it's also a valuable planning tool for ensuring availability of data to robustly support all product claims. For IVD medical devices, an outline of the different development phases including the sequence and means of determination of the scientific validity, the analytical and clinical performance shall be provided.

DATA: IDENTIFY PERTINENT DATA AND GAPS

The second step of a clinical/performance evaluation involves identifying data and potential data gaps. There are three evidence types required for evaluation of MDSW: (1) valid clinical association (MDR) / scientific validity (IVDR); (2) technical performance (MDR) / analytical performance (IVDR); and (3) clinical performance.

Valid clinical association / scientific validity

This ties the MDSW's output to an identified clinical parameter. More specifically, the evidence collected should support the association between a specific physiological state or condition and the MDSW's concept, conclusion or calculation

It's required to demonstrate the clinical significance of the MDSW to the intended healthcare situation in the real world. To be valid, it must be clinically accepted by the broader medical community, well-founded, and/or described in peer-reviewed scientific literature. Valid clinical association/scientific validity can be demonstrated by taking into account the current state-of-the-art, as well as existing clinical performance data, e.g., systematic scientific literature review, professional guidelines, technical standards, published clinical data, or the like. If these data are inadequate and/or gaps are identified, new evidence could be generated via e.g., analysis of real-world data or the manufacturer's own clinical studies[3].

[2] Known as Performance Evaluation Plan ("PEP") for IVDs and Clinical Evaluation Plan ("CEP") for general medical devices
[3] The term "clinical studies" is used to encompass both "clinical investigation" (general medical device) and "clinical performance study" (IVD).

Technical performance / analytical performance

This is the MDSW's first test in real-world environments and tests the accuracy, precision, and reliability of software performance, i.e., technical/analytical performance validation includes demonstration of the software's ability to correctly process data the same way, every time. Demonstrating technical/analytical performance also covers suitability of the software development processes, and implementation of standard software verification and validation processes in the overall software development process can satisfy this requirement.

Clinical performance

Clinical performance data are used to demonstrate that the claimed clinical outputs can be consistently obtained through use of the MDSW. The manufacturer needs to demonstrate that the MDSW has been tested under conditions such that evidence, or scientifically sound justification, support use in all: intended purpose(s), intended user(s), use condition(s), target population(s), and operating and use environment(s). For modularized software or multi-featured software (e.g., one that has differing and unique clinical benefits), validation may be conducted on a module or feature level. In this case, the clinical performance of each module or feature may be considered separately.

The method of clinical performance data generation should suit the MDSW characteristics and purpose, and can include pre-clinical testing or a clinical study. MDR-governed class III devices and implantable devices must include clinical investigation data, unless certain exceptions apply. For all devices under IVDR, regardless of class, clinical performance studies are required. Exceptions require 'due justification' for relying on other sources. For MDSW that doesn't claim outcomes that could be tested through clinical performance studies (i.e., non-measurable or non-patient relevant clinical outcomes), the clinical performance validation can be demonstrated similarly to technical performance: accurate, reliable output and usability. In all cases where clinical data are not included, this should be justified with reference to the risk management outcomes.

MDSW lifecycle management is key!

Software is generally improved during its lifecycle and, it's important for each update to determine the impact on clinical/performance evaluation. This involves considering the applicability of pre-clinical data, clinical data from pre-market investigations, post-market clinical follow-up and other post-market surveillance activities. Even if there's no impact, this should be documented, and if there's an impact, new clinical data may need to be generated.

ADDRESSING DATA GAPS: CLINICAL STUDIES FOR MDSW

To ensure the results of clinical studies demonstrate that the MDSW is safe and performs as intended, both the evaluation plan and clinical study plan(s) should be carefully thought-out. The design of clinical studies should be based on the intended purpose, clinical claims, and risk management results. Furthermore, the study should follow appropriate ethical requirements through compliance with Good Clinical Practice ("GCP"), as described in the standard EN ISO 14155 (for general medical devices) or EN[4] ISO 20916 (for IVDs) and be compliant with all other relevant legal and regulatory requirements. There are, however, differences between MDSW and other medical devices that should be considered when planning a MDSW clinical study:

- MDSW can often be used on a wide range of technical platforms (e.g., operating systems, hardware options, communication interfaces) and it's key to evaluate which alternatives need to be tested in the clinical study;

- MDSW usually doesn't come in direct contact with the patient – it may therefore be more relevant to evaluate the user than the patient, e.g., for a MDSW intended to display a 3D medical image as an adjunct to conventional images, it could be suitable to evaluate to what degree the user was helped in making a clinical diagnosis instead of evaluating the patient outcome after treatment; and

- retrospectively collected data is often more valuable than for other medical devices, as MDSW output is typically information instead of a direct action on a patient.

APPRAISAL: SCIENTIFIC VALIDITY, RELEVANCE AND WEIGHTING

The third step of a clinical/performance evaluation involves appraising the identified data sets. The appraisal should consider the methodological quality of the data and the relevance of the information. An appraisal plan will be defined to allow objective data set selection based on screening against inclusion and exclusion criteria. Included documents should be assessed based on pre-established appraisal critieria for clinical and pre-clinical data, such as software under evaluation, patient population, intended user, etc. The cumulative output of the appraisal should be systematically weighed according to the relative contribution to the clinical/performance evaluation, and ultimately for demonstrating conformance with the GSPRs.

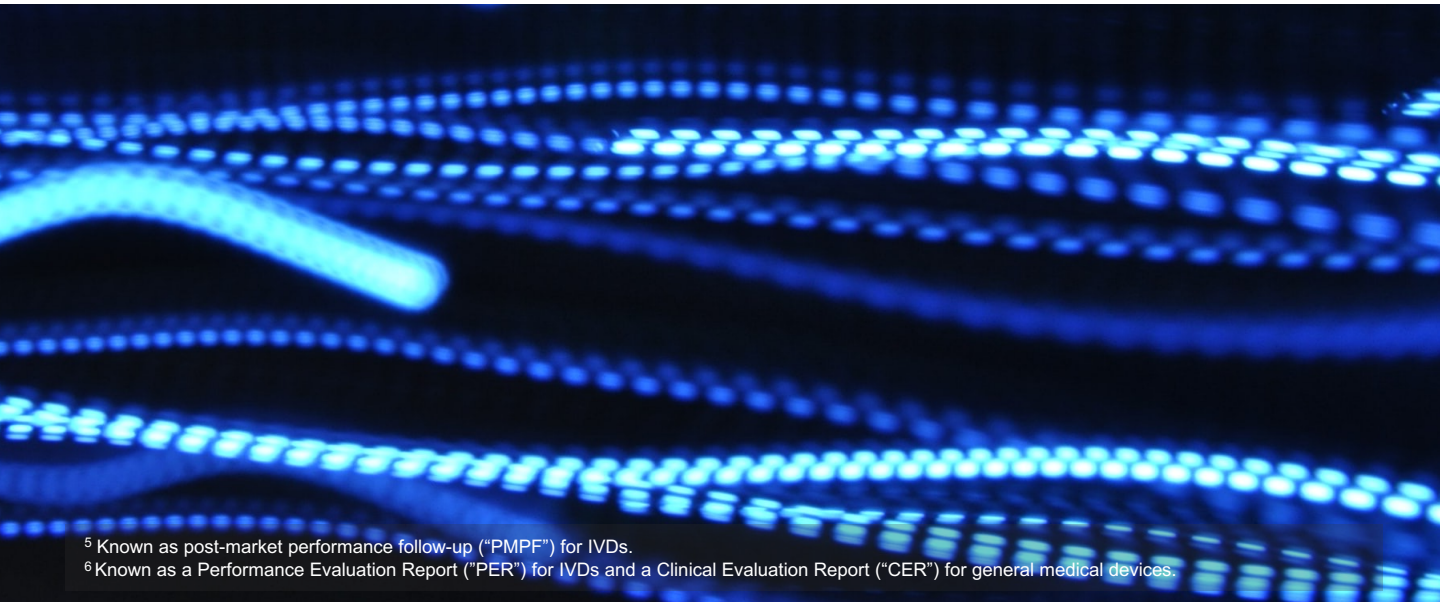
[4] EN version yet to be published. The standard is intended to become harmonized with the IVDR.

ANALYSIS: CONFORMITY WITH RELEVANT GSPRS

Analysis of pertinent data involves establishing there being enough data of sufficient quality given the characteristics of the MDSW, clinical risks, and intended purpose. The analysis should assess if there's alignment between the clinical/performance evaluation, the risk management outputs, and the information materials supplied by the manufacturer (e.g., instructions for use). This includes linking the output of the risk management process to the the clinical evidence identified during clinical/performance evaluation in a benefit-risk analysis. Gaps identified at this point may trigger data generation through e.g., an additional pre-market clinical study, or post-market clinical follow-up[5] ("PMCF") activities as part of post-market surveillance ("PMS"). Where demonstration of conformity with relevant GSPRs based on clinical data is not deemed appropriate, a clinical/performance evaluation still has to be performed. The absence of clinical data should be adequately justified based on the results of risk management and the specific device characteristics, the intended clinical performance and claims.

DOCUMENTATION: EVALUATION REPORT

The final step of a clinical/performance evaluation involves documenting the identified data, their appraisal and analysis, and resulting clinical evidence in an evaluation report[6]. The report should cover the three essential components discussed above: technical/analytical performance, valid clinical association/scientific validity, and clinical performance. The report should detail the evaluation process and its outcomes in a manner which allows it to be read and understood by an independent party, such as a notified body. Clinical/performance evaluation is an ongoing process to actively and continuously monitor the safety, effectiveness and performance of a MDSW, and the report should therefore be updated at regular, predefined intervals.



[5] Known as post-market performance follow-up ("PMPF") for IVDs.
[6] Known as a Performance Evaluation Report ("PER") for IVDs and a Clinical Evaluation Report ("CER") for general medical devices.

SUMMARY

- All medical devices, regardless of risk classification, require clinical/performance evaluation, but the unique properties of MDSW have implications for evaluation conduct, which have been taken into consideration in the EU guidance **MDCG 2020-1.** The guidance is valuable, but not a replacement for medically and scientifically competent evaluators.

- The MDSW characteristics are especially important when determining the type and amount of data needed to support the intended purpose and clinical claims. If clinical data are not included, this needs to be justified with reference to the risk management outcomes and specific device characteristics.

- If data gaps are identified, new data may need to be generated through a clinical study.

- Identified data sets should undergo a structured and objective appraisal to determine scientific validity, relevance and weighting. The pertinent data are analysed to conclude if conformance with relevant GSPRs has been demonstrated, if the information materials provided by the manufacturer are sufficient, and if there are any uncertainties to be addressed during PMS activities.

- The outcome of the evaluation shall be captured in a report, which is to be updated regularly as part of an ongoing process, conducted throughout the lifecycle of the MDSW.

NEED HELP WITH REGULATORY COMPLIANCE?

Clarvin, **Devicia**, **Kickfile** and **Morris Law** – a group of Life Science experts – offer full service for all your medical device compliance needs. We can advise you on clinical and regulatory strategies for your medical device, and can support you with everything from agreements, clinical investigation strategy and design, implementation of Quality Management Systems, and in establishing Technical Documentation for your device.