Brazilian Health Surveillance Agency – ANVISA

General Management of Technology of Health Products – GGTPS

TECHNICAL NOTE NO. 004/2016/GGTPS/DIREG/ANVISA

Object: Requirements to determine the need for clinical trials and guidelines for submission of data on safety and effectiveness for the purposes of *registro* and *cadastro* of health products at the General Management of Technology of Health Products.

The General Management of Technology of Health Products provides information about the need for submission of clinical trials for the purposes of *registro* and *cadastro* of health equipment and materials to the regulated sector:

The Resolution RDC no. 56/2001, which establishes the need of compliance with essential requirements of safety and effectiveness of health products, determines that these requirements must be based on clinical data, especially for health products of risk class III or IV, as follows:

"a) compilation of scientific bibliography of indexed publications related to clinical researches on the product's intended use and, if applicable, related to written reports containing a critical review of this bibliography; or

b) results and conclusions of a clinical research specifically conducted on the product."

The Resolution RDC no. 40/2015, which determines the requirements of registration of medical products, establishes in Article 4, Paragraph 1, that:

"For technical reasons, in order to prove the safety and effectiveness of the products due to potential public health risks, and for those products considered strategic by the Ministry of Health, ANVISA may request the submission of additional documentation and information."

Considering that, according to the legislation in force, health products must have proven safety and effectiveness; the company shall submit a specific clinical testing with the product to be registered by this Management in order to prove its safety and effectiveness in the following situations:

I – Innovative health products, regardless of their risk class (innovation in design, raw material, indications for use, among others);

II – Health products of risk class III and IV that require safety and effectiveness verification using specific clinical data of the product submitted, due to their unique nature and performance linked to the material design and manufacturing process. Examples: drug-

eluting stents and balloons, absorbable platforms, disc prostheses, interspinous devices, non-rigid fixation devices for spinal osteosynthesis, implantable materials in orthopedics with parameters different from those provided in the applicable technical standard, implantable cardiac pacemakers and defibrillators, among others.

In these cases, a clinical assessment report must be submitted at the time of application for *registro* or *cadastro*, contemplating clinical trial(s) that provides valid and sufficient scientific evidence for verification and confirmation of the safety and effectiveness of the target product of submission. Due to the variety of health products in the market, several methodologies and study designs can be used to prove the safety and effectiveness of a medical product. The specificities of the product and risks associated with its use shall be taken into account, thus contemplating randomized clinical trials with control group, single arm studies or even consistent and well-documented series of case studies. The selected methodology must be appropriate to provide valid safety measures and clinical performance. The level of evidence required to approve the product will depend on its indication for use, characteristics of the device, its level of innovation, among other aspects. Feasibility studies, isolated case studies and reports with lack of information that do not allow a proper assessment will not be qualified as confirmatory scientific evidence of safety and effectiveness.

In general, the clinical development of a health product is divided into the following phases: pilot and pivotal. The purpose of the pilot or feasibility phase, which begins with the first clinical use of the product, is to establish the safety of the product, initial parameters of effectiveness, and assist in the development of the subsequent pivotal study. The pivotal study confirms that the product is safe and effective for its target population. Pivotal studies are usually well-controlled experimental studies using either control or partially controlled groups. Pivotal clinical studies with confirmatory methodological characteristics of safety and effectiveness will be requested in order to obtain the *registro* and *cadastro*. Non-pivotal studies may be accepted in some cases, depending on the specificity of the product, as previously clarified (e.g. health products indicated to treat a rare clinical condition).

Clinical trials must include clinical condition(s) and target population for the medical products. The duration of the clinical study shall be adjusted to assess the expected effectiveness of the product as well as the occurrence of events and acute and late side effects. Robust outcomes shall be used, preferably clinical endpoints or the combination of clinical and surrogate or imaging endpoints, and the study design shall contain the methodology that allows a direct relation between the findings and the performance of the product tested. The rationale shall be demonstrated in order to determine the sample size of the study (number of participants), and the same must be obtained through statistical grounds and adjusted to the clinical development stage of the product.

The results of clinical trial(s) shall be submitted to this Management in the form of report, as well as publications in scientific journals related to these trials, if already available in the scientific literature. This Management recommends that the following information must be contained in the documentation, when applicable:

- Objectives of the research;
- Description of the study design;
- Inclusion and exclusion criteria;
- Hypothesis of the study;

- Definition of primary and secondary outcomes (safety and effectiveness endpoints);
- Criteria for the study success;
- Allocation of type I error (alpha) for the hypothesis evaluated;
- Type II error;
- Demonstration of the statistical analysis plan;
- Rationale to determine the sample size;
- Statistical methods used;
- Submission of results and data evaluation;
- Safety and effectiveness evaluation plan for the ITT population (intention-to-treat) or PP population (per protocol);
- Method, in case of blinding;
- Evaluation of adverse events; and
- Conclusion and considerations on study limitations.

We hereby highlight that each clinical study has specific characteristics. Therefore, some of the topics listed above may not be applicable to certain study designs. In these cases, the company must submit a justification for the lack of any of the aforementioned methodological guidelines. The items indicated do not fulfill all the attributes and information that can be requested for a clinical study. The company/sponsor/research institution has the autonomy to report the research according to its standards, however, more information will be requested whenever more details or details of the clinical data presented are needed.

It is important to emphasize that even studies with proper methodological characteristics and performed with the required scientific rigor may not provide sufficient results to demonstrate the safety and effectiveness. The methodology of the study and its results will be evaluated. In these cases, additional studies may be required.

Finally, the studies submitted to this Management must comply with ethical and Good Clinical Practices principles. Clinical trials performed in Brazil shall comply with RDC no. 10/2015 or the standards that preceded it. It is relevant to highlight that all clinical trials performed in Brazil and involving medical products, which are intended to support future *registro* or *cadastro*, shall have the SPECIAL COMMUNIQUÉ (*Comunicado Especial* in Portuguese) [clinical trials performed with health products of risk class III or IV] or SPECIFIC SPECIAL COMMUNIQUÉ (*Comunicado Especial Específico* in Portuguese) [clinical trials performed with health products of risk class I or II] from ANVISA authorizing the performance of these clinical trials. Therefore, if a clinical trial is identified with these characteristics, the lack of “communiqués” in the registration dossier may lead to a technical requirement or invalidation of the data for the purposes of *registro* or *cadastro*.

Brasilia, November 23rd, 2016

Management of Technology of Health Products

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