



PROPOSED DOCUMENT
Global Harmonization Task Force

Title: Post-Market Clinical Follow-Up Studies

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Preface

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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1 1. INTRODUCTION

2

3 While clinical evidence is an essential element of the pre-market conformity
4 assessment process to demonstrate conformity to Essential Principles, it is important
5 to recognise that there may be limitations in the clinical data available in the pre-
6 market phase. Such limitations may be due to, for example, the duration of pre-
7 market clinical investigations, the number of subjects involved in an investigation, the
8 relative homogeneity of subjects and investigators and the control of variables in the
9 setting of a clinical investigation versus use in the full range of conditions
10 encountered in general medical practice.

11

12 It is appropriate to place a product on the market once conformity to the relevant
13 Essential Principles, including a favourable risk/benefit ratio, has been demonstrated.
14 Complete characterization of all risks may not always be possible or practicable in the
15 pre-market phase. Therefore, there may be questions regarding residual risks that
16 should be answered in the post-market phase through the use of one or more
17 systematic post-market clinical follow-up studies. Such studies are not intended to
18 substitute or duplicate but rather supplement the pre-market clinical evaluation.

19

20 Post-market clinical follow-up studies are one of several options available in a post-
21 market surveillance programme (see GHTF SG2N47) and contribute to the risk
22 management process.

23

24

25 2. SCOPE

26

27 This document is intended to provide guidance on post-market clinical follow-up
28 studies developed specifically for issues of residual risk (including those mandated by
29 regulation). However, the principles presented may be applicable to post-market
30 clinical follow-up studies conducted for other purposes.

31 This document does not impose new regulatory requirements but is intended to
32 provide guidance on the appropriate use and conduct of post-market clinical follow-
33 up studies.

34
35 This document provides guidance in relation to:

- 36 i) the circumstances where a post-market clinical follow-up study is indicated;
37 ii) the general principles of post-market clinical follow-up studies involving
38 medical devices; and
39 iii) the use of study information.

40

41 This document does not apply to *in vitro* diagnostic devices.

42

43

44 **3. REFERENCES**

45

46 **GHTF Final Documents:**

- 47 SG1N41:2005 [Essential Principles of Safety & Performance of Medical Devices](#)
48 SG1N44:2008 [The Role of Standards in the Assessment of Medical Devices](#)
49 SG2N47:2005 [Review of Current Requirements on Post-Market Surveillance](#)
50 SG5N1:2007 [Clinical Evidence – Key Definitions and Concepts](#)
51 SG5N2:2007 [Clinical Evaluation](#)

52

53 **GHTF Proposed Documents:**

- 54 SG1(WD)N065 *Registration of Manufacturers and Other Parties and Listing of*
55 *Medical Devices*
56 SG5(PD)N3R7 [Clinical Investigations](#)

57

58 **International Standards:**

- 59 ISO 14155-1: 2003 [Clinical investigation of medical devices for human subjects –](#)
60 [Part 1 General requirements](#)
61
62 ISO 14155-2: 2003 [Clinical investigation of medical devices for human subjects –](#)
63 [Part 2 Clinical investigation plans](#)
64
65 ISO 14971: 2007 [Application of risk management to medical devices](#)

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Others:

Agency for Healthcare Research and Quality [Registries for Evaluating Patient Outcomes: A User's Guide](#)

72 **4. DEFINITIONS**

73
74

75 **Clinical Data:** Safety and/or performance information that are generated from the
76 clinical use of a medical device.

77

78 **Clinical Evaluation:** The assessment and analysis of clinical data pertaining to a
79 medical device to verify the clinical safety and performance of the device
80 when used as intended by the manufacturer.

81

82 **Clinical Evidence:** The clinical data and the clinical evaluation report pertaining to a
83 medical device.

84

85 **Clinical Investigation:** Any systematic investigation or study in or on one or more
86 human subjects, undertaken to assess the safety and/or performance of a
87 medical device.

88

89 **Device Registry:** An organized system that uses observational study methods to collect
90 defined clinical data under normal conditions of use relating to one or more devices
91 to evaluate specified outcomes for a population defined by a particular disease,
92 condition, or exposure and that serves (a) predetermined scientific, clinical or
93 policy purpose(s). (Agency for Healthcare Research and Quality, "Registries for
94 Evaluating Patient Outcomes: A User's Guide", modified)

95 Note: The term "device registry" as used here should not be confused with the concept of
96 device registration and listing. (See GHTF SG1N065)

97

98 **Post-market clinical follow-up study:** A study carried out following marketing
99 approval intended to answer specific questions relating to clinical safety or
100 performance (i.e. residual risks) of a device when used in accordance with its

101 approved labelling. These may examine issues such as long-term
102 performance, the appearance of clinical events (such as delayed
103 hypersensitivity reactions or thrombosis), or events specific to defined patient
104 populations.

105

106 **Residual Risk:** Risk remaining after risk control measures have been taken (ISO
107 14971) (e.g. known or emerging risks, or potential risks due to statistical
108 limitations).

109

110 **5. Circumstances Where A Post-Market Clinical Follow-Up Study Is** 111 **Indicated**

112 The need for post-market clinical follow-up studies should be determined from the
113 identification of residual risks that may impact the risk/benefit ratio.

114

115 Circumstances that may result in the need for post-market clinical follow-up studies
116 include, for example:

- 117 • innovation, e.g., where the design of the device, the materials, the
118 principles of operation, the technology or the medical indications are
119 novel;
- 120 • a new indication or claim has been approved;
- 121 • changes to device design or labelling;
- 122 • changes to medical practice;
- 123 • higher risk classification;
- 124 • high risk anatomical locations;
- 125 • severity of disease/treatment challenges;
- 126 • sensitivity of target population;
- 127 • identification of previously unstudied populations;
- 128 • risks identified from the literature or similar marketed devices;
- 129 • discrepancy between the pre-market follow-up time scales and the
130 expected life of the product;
- 131 • unanswered questions of long-term safety and performance;
- 132 • results of any previous clinical investigation including adverse events
133 identified or from post-market surveillance activities;

- 134 • questions of ability to generalise clinical investigation results; or
135 • emergence of new information relating to safety or performance.

136

137 Post-market clinical follow-up studies may not be required in cases where the
138 medium/long-term safety and clinical performance are already known from previous
139 use of the device or where other appropriate post-market surveillance activities would
140 provide sufficient data to address the risks.

141

142 **6. Elements Of A Post-Market Clinical Follow-Up Study**

143

144 Post-market clinical follow-up studies are performed on a device within its intended
145 use/purpose(s) according to the instructions for use. It is important to note that post-
146 market clinical follow-up studies must be conducted according to applicable laws and
147 regulations, and should follow appropriate guidance and standards.

148

149 The elements of a post-market clinical follow-up study include:

- 150 • (a) clearly stated objective(s)
151 • a scientifically sound design with an appropriate rationale and statistical
152 analysis plan
153 • a study plan
154 • implementation of the study according to the plan, an analysis of the data and
155 appropriate conclusion(s)

156

157 **The objective(s) of post-market clinical follow-up studies**

158 The objective(s) of the study should be stated clearly and should address the residual
159 risk(s) identified and be formulated to address one or more specific questions relating
160 to the clinical safety or performance of the device.

161

162 **The design of post-market clinical follow-up studies**

163 Post-market clinical follow-up studies should be designed to address the objective(s)
164 of the study. The design may vary based on the objective(s) and should be
165 scientifically sound to allow for valid conclusions to be drawn.

166

167 The study design can take several forms, for example:

- 168 • the extended follow-up of patients enrolled in pre-market investigations;
- 169 • a new clinical investigation;
- 170 • a review of data derived from a device registry; or
- 171 • a review of relevant retrospective data from patients previously exposed to the
- 172 device.

173

174 **The post-market clinical follow-up study plan**

175 All post-market clinical follow-up studies should have a plan appropriate for
176 addressing the stated objectives. The study plan should justify, for example:

- 177 • the patient population;
- 178 • the selection of sites and investigators;
- 179 • the endpoints and statistical considerations;
- 180 • the number of subjects involved;
- 181 • the duration of the study;
- 182 • the data to be collected;
- 183 • the analysis plan including any interim reporting; and
- 184 • procedures for early study termination.

185

186 **Implementation of the post-market clinical follow-up study, analysis of data and** 187 **conclusion(s)**

188 The study should:

- 189 • be executed with adequate control measures to assure compliance with the plan;
- 190 • include data analysis with conclusions drawn according to the analysis plan by
- 191 someone with appropriate expertise; and
- 192 • have a final report with conclusions relating back to original objective(s).

193

194 **7. The Use of Study Information**

195 The data and conclusions derived from the post-market clinical follow-up study are
196 used to provide clinical evidence to support the post-market surveillance program.

197 This process may result in the need to reassess whether the device continues to
198 comply with the Essential Principles. Such assessment may result in corrective or

199 preventive actions, for example, changes to the labelling/instructions for use, changes
200 to manufacturing processes, or changes to the device design.
201