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A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

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1 A Multicenter Prospective Observational Study Protocol for Radiation Exposure
2 from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

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79 **Keywords:** Radiation Exposure, Diagnostic Reference Levels, ERCP, Gastrointestinal
80 Fluoroscopic Procedure, Endoscopy.

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6 **82 ABSTRACT**

7
8 **83 INTRODUCTION:** Recently, the use of various endoscopic procedures under X-ray
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11 **84** fluoroscopic guidance, such as endoscopic retrograde cholangiopancreatography
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13 **85** (ERCP), interventional endoscopic ultrasonography (EUS), enteral endoscopy, and
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16 **86** stenting, has been rapidly increasing because of the minimally invasive nature of these
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18 **87** procedures compared to that of surgical intervention. With the spread of computed
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21 **88** tomography and fluoroscopic interventions, including endoscopic procedures under X-
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24 **89** ray guidance, high levels of radiation exposure (RE) from medical imaging have led to
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26 **90** major concerns throughout society. However, information about RE related to these
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28 **91** image-guided procedures is scarce, and their reference levels have not been
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31 **92** established. The aim of this study is prospectively to collect the actual RE dose and to
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34 **93** help establish diagnostic reference levels (DRLs) in the field of gastroenterology in
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36 **94** Japan.

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38 **95 METHODS AND ANALYSIS:** This study is a multicenter, prospective observational
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41 **96** study that aims to collect the actual RE from treatments and diagnostic procedures,
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44 **97** including ERCP, interventional EUS, balloon-assisted enteroscopy, and enteral metallic
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46 **98** stent and enteral tube placement. We will measure the total fluoroscopy time (FT, min),
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48 **99** the total dose-area product (DAP, Gy cm^2) and air-kerma (AK, mGy) of those
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51 **100** procedures. Because we will be collecting the actual RE data and identifying the
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54 **101** affecting factors through a prospective, nationwide design, this study will help to set the
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56 **102** DRLs of ERCP, interventional EUS, balloon-assisted enteroscopy, and enteral metallic
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58 **103** stent and enteral tube placement.
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6 104 **ETHICS AND DISSEMINATION:** This trial (Radiation EXposure from GastroIntestinal
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9 105 fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials
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11 106 Registry at <http://www.umin.ac.jp/ctr/> with number UMIN000036525 (registered 1 May
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14 107 2019). Approval was obtained from each institutional review board. The requirement for
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16 108 informed consent will be waived via the *opt-out* method of each hospital website.
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6 110 **Article summary**
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8 111 This is a research protocol of a study that aims to collect actual data on radiation
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10 112 exposure (RE) and to identify the factors affecting RE during treatments and diagnostic
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12 113 procedures under different types of fluoroscopic guidance for gastroenterology
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15 114 procedures, including the gastrointestinal, hepatobiliary and pancreatic fields, to serve
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18 115 as a basis for DRLs in Japan.
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23 117 **Strengths and limitations of this study**
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26 118 • A large, multicenter, nationwide dataset of radiation exposure doses for
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28 119 gastrointestinal fluoroscopic procedures, including endoscopic retrograde
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30 120 cholangiopancreatography, interventional endoscopic ultrasonography, balloon-
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32 121 assisted enteroscopy, and enteral metallic stent and enteral tube placement, serves
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34 122 as a basis for the diagnostic reference levels in Japan.
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36 123 • This study will include data from relatively recently launched fluoroscopic systems.
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38 124 Therefore, these data may not always be valid for old models of fluoroscopic
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40 125 systems.
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42 126 • This study will be conducted in hospitals where gastroenterologists or endoscopists
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44 127 who are concerned about medical radiation exposure work. Therefore, the collected
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46 128 values of radiation exposure may be lower than those in the real world.
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130 INTRODUCTION

131 Medical radiation is widely used in both medical imaging and radiation treatment. In
132 medical imaging, fluoroscopy employs radiation to show a continuous X-ray image on a
133 monitor and plays a major role in the daily practices of gastroenterology, digestive
134 endoscopy, and hepatobiliary and pancreatic studies. Radiological medical imaging
135 has both benefits and drawbacks for patients. The latter is split into two types:
136 deterministic risks ¹, determined by the threshold dose, as represented by skin injury;
137 and stochastic risks, determined by a linear no-threshold model, such as cancer risk ².
138 Therefore, all medical staff involved in medical radiation are required to have correct
139 knowledge of the appropriate use of medical radiation. Historically, medical radiation
140 has rapidly increased since the 1990s with the spread of computed tomography (CT),
141 and radiation-associated cancer risk was recognized in the same period, even with
142 small doses ^{3 4 5}. In particular, the use of CT has increased approximately 12-fold in the
143 United Kingdom and more than 20-fold in the United States in the last 25 years ⁶.
144 The International Atomic Energy Agency (IAEA), the International Commission on
145 Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects
146 of Atomic Radiation (UNSCEAR), and other radiological societies have been trying to
147 manage medical RE according to the “as low as reasonably achievable” (ALARA)
148 principle by establishing diagnostic reference levels (DRLs) to optimize protection from
149 medical radiation. The concept of DRLs was first introduced by ICRP 73 ⁷ in 1996.
150 Then, the ICRP emphasized the important role of DRLs as a tool for optimizing patient
151 protection ^{8 9}. Accordingly, the ICRP set specific target levels for various X-ray-related

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6 152 procedures in 2007⁸. This movement of setting DRLs has been led by radiation-related
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8 153 societies in each region, although mainly in Western countries. The ICRP 135
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11 154 recommends that all individuals who are involved in patient procedures with the risk of
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14 155 medical exposure should be familiar with the DRL process as a tool for optimizing
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16 156 protection¹⁰. DRLs are now widely accepted in not only Western countries but also
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18 157 Japan (Japan DRLs 2015)¹¹, and DRLs have been the global standard for all
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21 158 procedures that use ionizing radiation. The introduction of DRLs in the UK could
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24 159 achieve a reduction in radiation dose of approximately 50% in typical X-ray
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26 160 examinations over 15 years¹². However, there is still not enough available data on RE
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29 161 for gastrointestinal fluoroscopic procedures, such as endoscopic retrograde
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31 162 cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS),
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34 163 small bowel endoscopy, and enteral stent placement; these techniques are still being
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36 164 developed and have recently been used with increasing frequency¹³.
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39 165 Our gastroenterologists and endoscopists are still unfamiliar with the DRL concept.
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41 166 Among gastrointestinal endoscopy associations, the 2012 European Gastrointestinal
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44 167 Endoscopy Society (ESGE) guidelines for radiation protection states that the entrance
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46 168 skin dose (ESD; approximately equivalent to air-kerma in this study) and kerma-area
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49 169 product (KAP; approximately equivalent to dose-area product (DAP) in this study)
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51 170 during ERCP are 55-347 mGy and 3-115/8-333 Gy cm^2 , respectively, although
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54 171 information regarding DRLs of ERCP is limited because this statement is based on
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56 172 approximately only 600 cases of ERCP, including 7 reports¹⁴. No guidelines on RE
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59 173 from the American Society for Gastrointestinal Endoscopy (ASGE) exist, but the ASGE
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6 174 recommends measuring and documenting fluoroscopy time (FT) and radiation dose in
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9 175 all ERCP procedures as a quality indicator (level of evidence: 2C) ¹⁵. Although no
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11 176 guidelines for exposure have been developed at the Japan Gastroenterological
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13 177 Endoscopy Society (JGES), a description of FT exists in the item about ERCP in the
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15 178 Japan Endoscopy Database (JED) ¹⁶, which is scheduled to be implemented as a
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17 179 nationwide endoscopic survey in 2020. Therefore, we aim to collect the actual RE data
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19 180 and identify the affecting factors in the REX-GI study and to establish data based on
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21 181 the DRLs of ERCP, interventional EUS, balloon-assisted enteroscopy, and enteral
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23 182 metallic stent and enteral tube placement.
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6 183 **METHODS AND ANALYSIS**
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8 184 **Aims**
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11 185 The primary aim of this nationwide, prospective study is to collect actual data on RE
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13 186 and identify the factors affecting RE during treatments and diagnostic procedures
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16 187 under different types of fluoroscopic guidance for gastroenterology procedures,
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18 188 including the gastrointestinal, hepatobiliary and pancreatic fields, to serve as a basis
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21 189 for DRLs in Japan.
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26 191 **Design**
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28 192 This is a multicenter, prospective observational cohort study of consecutive patients
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31 193 who underwent the following 5 treatments and diagnostic procedures under
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33 194 fluoroscopic guidance in the field of gastroenterology: 1) ERCP, 2) interventional EUS,
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36 195 3) balloon-assisted enteroscopy, 4) enteral metallic stent placement; and 5) enteral
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38 196 tube placement. We examined the procedure time (min), total FT (min), AK (mGy),
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41 197 DAP (Gycm²), total number of roentgenography, and radiation dose rate (RDR)
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43 198 (mGy/min) during the procedures. The participating clinicians will manage patients
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46 199 according to usual clinical practice, and the patients will undergo the above 5
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48 200 procedures. For analysis, all data, including the related variables and outcome data
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51 201 (Tables 1 and 2), will be collected for all patients. The study (Radiation EXposure from
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53 202 GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN
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56 203 Clinical Trials Registry at <http://www.umin.ac.jp/ctr/> with number UMIN000036525
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58 204 (registered 1 May 2019).
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8 **206 Setting**

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11 207 The study was conducted at 7 university hospitals, 4 cancer centers, 9 general
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13 208 hospitals and 2 municipal hospitals in Japan. The participating hospitals are Toyonaka
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15 209 Municipal Hospital, Kindai University, the University of Tokyo, Fukui Prefectural
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17 210 Hospital, Kansai Rosai Hospital, Osaka City University, Ishikawa Prefectural Central
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19 211 Hospital, Tonan Hospital, Japanese Foundation for Cancer Research, Suita Municipal
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21 212 Hospital, Osaka Rosai Hospital, Osaka General Medical Center, Fukushima Medical
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23 213 University School of Medicine, Hyogo Cancer Center, Kitano Hospital, Tane General
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25 214 Hospital, Japanese Red Cross Medical Center, Kure Medical Center and Chugoku
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27 215 Cancer Center, Nagoya City University Hospital, Toho University Ohashi Medical
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29 216 Center, Osaka International Cancer Institute, and Gifu University Hospital (Figure 1).

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31 217 The central sites of the study are located at the Toyonaka Municipal Hospital and
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33 218 Kindai University.

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43 **220 Study population**

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46 221 We will include all patients following usual clinical care who underwent the following
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48 222 treatments and diagnostic procedures under fluoroscopic guidance: 1) ERCP; 2)
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50 223 interventional EUS; 3) balloon-assisted enteroscopy; 4) enteral metallic stent
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52 224 placement; and 5) enteral tube placement. There is no age restriction. We will exclude
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54 225 patients who do not want to participate in this study via the *opt-out* method of each
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6 226 hospital website and patients who the attending physicians judge inadequate for this
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8 227 study.

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13 229 **Primary outcomes**

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16 230 The primary outcomes will be the total FT (min), RDR (mGy/min), dose-area
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18 231 parameters (AK (mGy) and DAP (Gycm²)) and total number of imaging studies that the
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20 232 patients who meet the individual inclusion and exclusion criteria will undergo (Table 1).
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26 234 **Secondary outcomes**

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28 235 The secondary outcome will be the RE-related factors that affect the radiation dose in
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30 236 each procedure. The details are shown in Table 2.
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36 238 **Setting the sample size**

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38 239 According to the preliminary questionnaire survey (data not shown), the numbers of
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40 240 examinations per year in the 8 centers that plan to participate in March 2019 are 4000
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42 241 ERCP procedures, 125 EUS procedures, 320 small intestine endoscopy procedures,
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44 242 44 esophageal stent placements, 150 gastroduodenal stent placements, 75 colorectal
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46 243 stent placements, 180 transanal ileus tube placements, and 75 ileus tube placements.
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48 244 To set the DRL and to reduce intraprocedural variability in each hospital, we believe
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50 245 that initially enrolling a high number of facilities and patients is desirable; therefore, we
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52 246 did not set an upper limit for the goals.
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6 248 **Data analysis plan**
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8 249 Continuous variables will be expressed as medians with interquartile ranges. The
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10 250 categorical variables will be expressed as numbers in each category or as frequencies.
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13 251 Simple linear regression analysis will be performed to identify the relationships
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16 252 between procedure time, FT and RD. A multiple linear regression analysis will be
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18 253 performed to identify the factors related to RD. A P value of 0.05 will be considered
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21 254 statistically significant. All statistical analyses will be performed with JMP software
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24 255 (SAS Institute, Inc., Cary, NC, USA).
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29 257 **Patient and public involvement and patient recruitment**
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31 258 Clinical factors related to ERCP and interventional EUS have been retrospectively
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33 259 collected at two sites (Toyonaka Municipal Hospital and Kindai University)¹⁷⁻²⁰. We
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36 260 used those published data to develop plans for the design or implementation of the
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38 261 study and to determine the research question or the outcome measures. No patients
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41 262 were requested to advise us on the interpretation or writing up of results. There are no
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44 263 plans to disseminate the results of the research to study participants, but we will
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46 264 consider disseminating the results of the research to the relevant patient community.
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51 266 **Data collection**
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53 267 The clinical factors have been modified to comply with local patient flow and
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56 268 administrative requirements and have been assessed and approved by the study
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59 269 steering committee. Case report forms will be de-identified after all data points have
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6 270 been completed and all data queries have been addressed. Data collection will be
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9 271 scheduled to be performed at 3-month intervals to prevent data loss. Data analysis will
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11 272 take place at the central study site (Kindai University). This study does not require data
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13 273 monitoring due to its nature as an observational study without interventions. Data will
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16 274 be retained for either a minimum of 5 years after the end of the study or for 10 years
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18 275 after publication, whichever is later.
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22 277 **Time plan**

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26 278 May 2019 - December 2020: Patient recruitment.

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29 279 2021: Data analysis and writing and submission of the main manuscript for publication.
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33 281 **Ethics and dissemination**

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36 282 This observational study will be conducted in accordance with the Declaration of

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39 283 Helsinki, and approval has been obtained from each institutional review board. The

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42 284 requirement for informed consent will be waived via the *opt-out* method of each

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48 49 287 **Author contributions**

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53 288 Nishida T, Hayashi S (Toyonaka Municipal Hospital), and Takenaka M (Kindai

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55 289 University) designed this study. Hosono M (Kindai University) critically reviewed the

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58 290 protocol. Nishida T, Hayashi S (Toyonaka Municipal Hospital), Takenaka M (Kindai
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8 292 Hospital), Yamaguchi S (Kansai Rosai Hospital), Maruyama H (Osaka City University),
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13 294 (Cancer Institute Hospital, Japanese Foundation for Cancer Research), Nagaike K
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16 295 (Suita Municipal Hospital), Yamada T (Osaka-Rosai Hospital), Yakushijin T (Osaka
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18 296 General Medical Center), Takagi T (Fukushima Medical University School of Medicine),
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21 297 Tsumura H (Hyogo Cancer Center), Kurita A (Kitano Hospital), Asai S (Tane General
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23 298 Hospital), Ito Y (Japanese Red Cross Medical Center), Kuwai T (National Hospital
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26 299 Organization, Kure Medical Center and Chugoku Cancer Center), Hori Y (Nagoya City
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30 301 Medical Center), Ikezawa K (Osaka International Cancer Institute), Iwashita T (Gifu
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32 302 University Hospital), Matsumoto K, and Inada M (Toyonaka Municipal Hospital)
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36 303 participated this study and will recruit the patients. All authors accepted the final
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38 304 version of the protocol (ver. 1.1: 2019-Mar-14, ver.1.5: 2019-July-15).
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14 315 Hospital), Tetsuya Sumiyoshi (Tonan Hospital), Takashi Sasaki, Atsuko Tamashiro,
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18 317 Research), Takumi Kanagawa, Yuichi Yoshida, Masafumi Naito (Suita Municipal
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21 318 Hospital), Shuji Ishii (Osaka General Medical Center), Takuto Hikichi (Fukushima
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31 322 (Nagoya City University Graduate School of Medical Sciences), Hiroaki Shigoka (Toho
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34 323 University Ohashi Medical Center).

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43 327 commercial or not-for-profit sectors.
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48 49 329 **Publication and data sharing**

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53 330 After completion of the study, a main manuscript will be prepared to present the results
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55 331 and will be submitted to a clinical journal for peer review. This study will ensure that the
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58 332 public has access to the published data. A file containing the clean dataset used for
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6 333 final analysis to determine the main data of the study, and an explanation of variables

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8 334 will be made publicly accessible in an anonymized format.

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13 336 **Consent for publication**

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16 337 The principal investigators will form a publication committee, which will include key

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18 338 members of this study, and the committee will grant authorship according to individual

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20 339 input. Investigators who do not qualify for authorship will be acknowledged by name in

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22 340 the final manuscript.

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31 342 **Conflicts of interest statement.**

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35 343 None of the authors have any competing interests arising from this research.

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6 **345 Discussion**
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9 **346** Currently, the establishment of DRLs is an international requirement for protection from
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11 **347** medical radiation. Generally, for diagnostic radiology, national and regional DRLs are
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13 **348** usually set at the 75% percentile of the distribution of a typical sample dose ²¹. All
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16 **349** physicians or medical staff who are involved in radiological imaging or procedures
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18 **350** under fluoroscopic guidance should be familiar with the DRL process as a tool for
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21 **351** optimizing protection. In addition, separate DRLs must be established for each country
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24 **352** and/or region because the equipment and procedure protocols can vary among
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26 **353** different regions ²¹. However, the amount of RE depends on procedure complexity,
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28 **354** patient anatomy, lesion characteristics, disease severity ¹⁰ and type of fluoroscopic
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31 **355** devices ¹⁸; thus, setting the upper limit of radiation use by applying uniform standards is
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34 **356** difficult. Generally, DRLs are not dose limits and do not help distinguish between good
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36 **357** and poor medical practices ²¹. Therefore, a high demand exists for a large amount of
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39 **358** real-world evidence. The 2015 Japan DRLs state that the methods for establishing
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42 **359** DRLs not only includes setting radiation dose levels but also includes determining the
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44 **360** dose quantities and units used to set the DRLs, thus standardizing the methodology for
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46 **361** dose measurements, data collection and identification of the applications of DRLs ¹¹.
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49 **362** Unfortunately, most gastroenterologists are unfamiliar with not only DRLs but also
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52 **363** radiation protection because information on RE from gastrointestinal medical treatment
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54 **364** is currently very scarce, and few RE standards, including DRLs, have been established
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56 **365** worldwide. Given this background, the REX-GI study is planned as an observational,
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59 **366** nationwide study in Japan. Our results will help to promote radiation optimization and
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6 367 patient radiation protection in gastroenterology studies, such as digestive endoscopy,
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9 368 and hepatobiliary and pancreatic procedures.
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Table 1. Primary outcomes

Factors	Variables
Patients	<ul style="list-style-type: none"> ▪ Procedure type ▪ Age ▪ Sex
Fluoroscopic system	<ul style="list-style-type: none"> ▪ Fluoroscopic device (company, device model, manufacturing year) ▪ Basic use setting: frame per second (FPS), radiation field (cm²)
Radiation exposure	<ul style="list-style-type: none"> ▪ Total fluoroscopy time (FT) (min) ▪ Air-Kerma (AK) (mGy) ▪ Dose-area product (DAP) (Gycm²) ▪ Total number of roentgenography procedures ▪ Radiation dose rate (RDR) (mGy/min)

Table 2. Secondary outcomes

Procedures	Radiation exposure-related factors
ERCP	<p>(A) Surgically altered gastrointestinal anatomy</p> <p>Billroth I reconstruction, Billroth II reconstruction, Roux-en-Y reconstruction, pancreaticoduodenectomy</p> <p>(B) Type of endoscope</p> <p>(C) Naïve papilla</p> <p>(D) Indications for ERCP (including suspicion) are classified into the following five categories:</p> <ol style="list-style-type: none"> 1) Choledocholithiasis (maximum diameter, number of stones, presence of cholangitis, tube exchange for the above diseases, treatment for choledocholithiasis with or without balloon catheter, basket catheter, crusher, etc.) 2) Distant malignant bile duct stricture (papillary tumor, distal cholangiocarcinoma, pancreatic cancer, etc.) 3) Proximal malignant bile duct stricture (Hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, gallbladder cancer, etc.) 4) Pancreatic duct examination (pancreas cancer, intraductal papillary mucinous neoplasm, etc.) 5) Other diseases apart from those listed above (benign bile duct stricture, pancreatobiliary junction abnormality, etc.) <p>(E) Total procedure time (min) *</p> <ol style="list-style-type: none"> 1) Cannulation time

	<p>2) Treatment time</p> <p>(F) Experience of the high-volume endoscopist (HVE) or low-volume endoscopist: (LVE) †</p> <p>(G) Facility scale: The number of ERCP procedures per year</p> <p>(H) Whether the fluoroscopic operator is inside or outside in the fluoroscopy room</p> <p>(I) Various treatments (endoscopic sphincterotomy, stone treatment, bile duct pancreatic stent, cytology, biopsy, naïve papilla, cannulation method, contrast agent, intubation time, first-use catheter, large balloon, crusher, drainage area or method, stent type used, cholangioscopy)</p> <p>(J) Sedation: Medication and the depth of the anesthesia ‡</p>
Interventional EUS	<p>(A) Indication for interventional EUS (EUS-guided hepaticogastrostomy (HG)), choledochoduodenostomy (CDS), cyst drainage (CD), antegrade treatment (AG), rendezvous technique (RV), pancreatic duct drainage (PD)</p> <p>(B) Total procedure time ‡</p> <p>1) Endoscope insertion time</p> <p>2) Treatment time</p> <p>(C) Facility scale: The number of EUS interventions per year, the number of EUS-guided fine-needle aspiration (FNA) procedures per year</p> <p>(D) Double stenting (presence or absence of duodenal stenosis)</p> <p>(E) Device</p> <p>(F) Scope position</p> <p>(G) Sedation: Medication and the depth of anesthesia</p>
Balloon-assisted	<p>(A) Disease indicating balloon-assisted enteroscopy</p>

enteroscopy	<ol style="list-style-type: none"> 1) Hemostatic or bleeding confirmation 2) Crohn's disease 3) Small intestine tumor examination 4) Others <p>(B) Insertion site: perioral or transanal</p> <p>(C) Insertion length (cm)</p> <p>(D) Total procedure time (min)</p>
Enteral metallic stent placement	<p>(A) Stent location</p> <ol style="list-style-type: none"> 1) Esophagus (Upper/Mid-Low/Trans) 2) Gastro-duodenum (Above pylorus/Trans pylorus /Below pylorus) 3) Colon stent (Right/Left/Rectum) <p>(B) Total procedure time (min) §</p> <ol style="list-style-type: none"> 1) Endoscope insertion time 2) Treatment time
Enteral ileus tube placement	<p>(A) Disease indicating ileus tube</p> <p>(B) Intranasal ileus tube insertion for ileal obstruction or transanal ileus tube insertion for malignant colonic obstruction</p> <ol style="list-style-type: none"> 1) Tube insertion length for peroral ileus tube placement (cm) 2) The occlusion site for the transanal tube (Right/Left/Rectum) <p>(D) Total procedure time (min) §</p>

ERCP: endoscopic retrograde cholangiopancreatography

* Cannulation time is defined as the time from endoscope insertion until successful biliary cannulation, and treatment time was defined as the time from successful biliary cannulation until the scope was removed from the patient. The total procedure time was defined as the time from endoscope insertion until the scope was removed from the patient (cannulation time +treatment time).

‡ Depth of anesthesia is divided into 3 levels based on the Richmond Agitation-Sedation Scale (RASS), Ramsay Scale, and Sedation-Agitation Scale (SAS): good, poor, and very bad. The good level is defined as RASS score: -5 ~ -1, SAS score: 1 ~ 3, and Ramsay score: 3 ~ 6 equivalent, without additional unplanned doses. The poor level is defined as RASS score: 0 ~ + 1, SAS score: 4 ~ 5, and Ramsay score: 1 ~ 2, without physical restraint but with unplanned doses. The very bad level is defined as requiring physical restraint with a manpower considered dangerous, RASS score: +2 to +4, and SAS score: 6 to 7 regardless of Ramsay score.

† HVE: Endoscopists with more than 200 ERCP results and who have been involved in ERCP for over 10 years. LVE: Non-HVE endoscopists who perform ERCP.

‡ Endoscope insertion time is defined as the time from endoscope insertion until the initial EUS-guided needle puncture, and treatment time was defined as the time from initial EUS-guided needle puncture until the scope was removed from the patient. The total procedure time was defined as the time from endoscope insertion until the scope was removed from the patient (endoscope insertion time +treatment time).

‡ Endoscope insertion time is defined as the time from endoscope insertion until initial guidewire exploration, and treatment time was defined as the time from initial guidewire exploration until the scope was removed from the patient. The total procedure time was defined as the time from endoscope insertion until the scope was removed from the patient (endoscope insertion time +treatment time).

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6 **Figure legends**
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8 **Figure 1.** The participating hospitals in this study.
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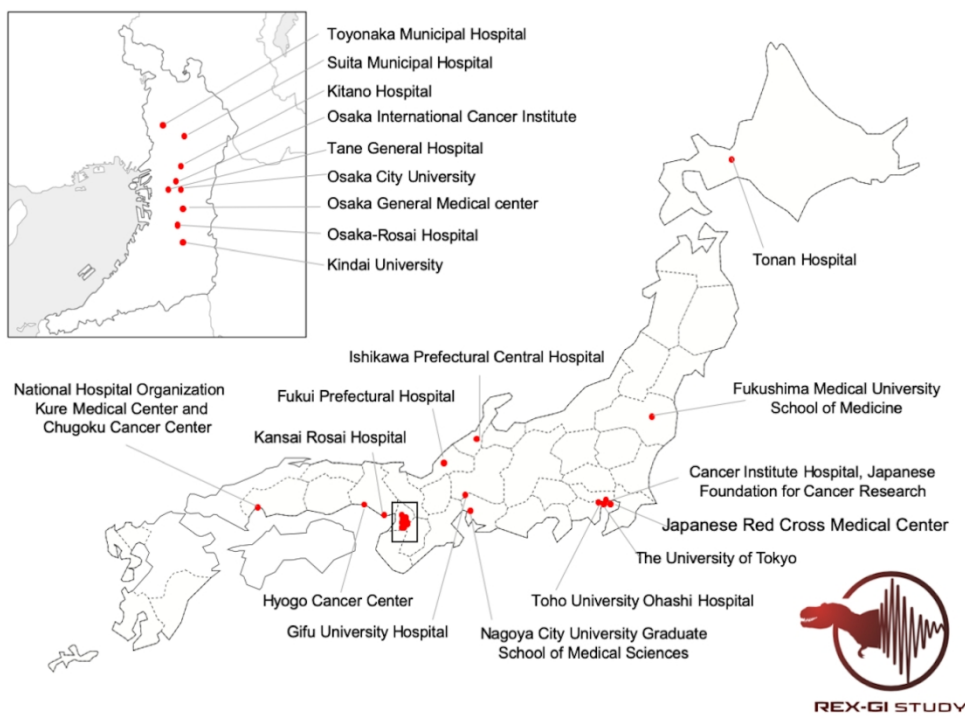


Figure 1. The participating hospitals in this study.

119x90mm (300 x 300 DPI)

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6, 11
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6, 11
Protocol version	#3	Date and version identifier	16
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

1	Roles and	#5b	Name and contact information for the trial sponsor	N.A.
2	responsibilities:			
3	sponsor contact			
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7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	N.A.
8	responsibilities:		collection, management, analysis, and interpretation of data;	
9	sponsor and funder		writing of the report; and the decision to submit the report for	
10			publication, including whether they will have ultimate authority	
11			over any of these activities	
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16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	12, 14
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for undertaking	8-10
27	rationale		the trial, including summary of relevant studies (published and	
28			unpublished) examining benefits and harms for each intervention	
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32	Background and	#6b	Explanation for choice of comparators	9
33	rationale: choice of			
34	comparators			
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37	Objectives	#7	Specific objectives or hypotheses	9-10
38				
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40	Trial design	#8	Description of trial design including type of trial (eg, parallel	11
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
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46	Methods:			
47	Participants,			
48	interventions, and			
49	outcomes			
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53	Study setting	#9	Description of study settings (eg, community clinic, academic	12
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N.A.
7	description			
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10	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N.A.
11	modifications			
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15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N.A.
16	adherence			
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20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N.A.
21	concomitant care			
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24	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
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34	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15
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40	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
41				
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45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
46				
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49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	N.A.
55	generation			
56				
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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3			
4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
9			
10			
11	Allocation:	#16c	Who will generate the allocation sequence, who will enrol
12	implementation		participants, and who will assign participants to interventions
13			
14			
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial
16			participants, care providers, outcome assessors, data analysts),
17			and how
18			
19			
20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
23			
24			
25	Methods: Data		
26	collection,		
27	management, and		
28	analysis		
29			
30			
31			
32	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
39			
40			
41			
42			
43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48			
49	Data management	#19	Plans for data entry, coding, security, and storage, including any
50			related processes to promote data quality (eg, double data entry;
51			range checks for data values). Reference to where details of data
52			management procedures can be found, if not in the protocol
53			
54			
55	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
58			
59			
60			

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	N.A.
2	analyses		analyses)	
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	15
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
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9				
10	Methods: Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	15
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
19				
20				
21				
22	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	15
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	N.A.
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
31				
32				
33	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	N.A.
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
37				
38	Ethics and			
39	dissemination			
40				
41				
42	Research ethics	#24	Plans for seeking research ethics committee / institutional review	15
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	N.A.
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
51				
52				
53	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	15
54			participants or authorised surrogates, and how (see Item 32)	
55				
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1	Consent or assent:	#26b	Additional consent provisions for collection and use of	N.A.
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
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5				
6	Confidentiality	#27	How personal information about potential and enrolled	14
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	#28	Financial and other competing interests for principal investigators	17, 18
12			for the overall trial and each study site	
13				
14				
15	Data access	#29	Statement of who will have access to the final trial dataset, and	17
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	N.A.
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results	14
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
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31				
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33	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	18
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	N.A.
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	Appendices			
42				
43	Informed consent	#32	Model consent form and other related documentation given to	N.A.
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N.A.
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
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BMJ Open

A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

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1 **A Multicenter Prospective Observational Study Protocol for Radiation Exposure**
2 **from Gastrointestinal Fluoroscopic Procedures (REX-GI study)**

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36 77 **Word count:** 2804 words
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41 79 **Keywords:** Radiation Exposure, Diagnostic Reference Levels, ERCP, Gastrointestinal
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43 80 Fluoroscopic Procedure, Endoscopy.
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6 **82 ABSTRACT**

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8 **83 INTRODUCTION:** Recently, the use of various endoscopic procedures under X-ray
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11 **84** fluoroscopic guidance, such as endoscopic retrograde cholangiopancreatography
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13 **85** (ERCP), interventional endoscopic ultrasonography (EUS), enteral endoscopy, and
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16 **86** stenting, has been rapidly increasing because of the minimally invasive nature of these
17
18 **87** procedures compared to that of surgical intervention. With the spread of computed
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20
21 **88** tomography and fluoroscopic interventions, including endoscopic procedures under X-
22
23
24 **89** ray guidance, high levels of radiation exposure (RE) from medical imaging have led to
25
26 **90** major concerns throughout society. However, information about RE related to these
27
28 **91** image-guided procedures in gastrointestinal endoscopy is scarce, and the RE
29
30
31 **92** reference levels have not been established. The aim of this study is to prospectively
32
33
34 **93** collect the actual RE dose and to help establish diagnostic reference levels (DRLs) in
35
36 **94** the field of gastroenterology in Japan.

37
38 **95 METHODS AND ANALYSIS:** This study is a multicenter, prospective observational
39
40
41 **96** study that is being conducted to collect the actual RE from treatments and diagnostic
42
43
44 **97** procedures, including ERCP, interventional EUS, balloon-assisted enteroscopy, enteral
45
46 **98** metallic stent placement and enteral tube placement. We will measure the total
47
48 **99** fluoroscopy time (FT, min), the total dose-area product (DAP, Gy cm^2) and air-kerma
49
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51 **100** (AK, mGy) of those procedures. Because we are collecting the actual RE data and
52
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54 **101** identifying the influential factors through a prospective, nationwide design, this study
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56 **102** will provided guidance regarding the DRLs of ERCP, interventional EUS, balloon-
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58 **103** assisted enteroscopy, enteral metallic stent placement and enteral tube placement.
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6 104 **ETHICS AND DISSEMINATION:** This trial (Radiation EXposure from GastroIntestinal
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8
9 105 fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials
10
11 106 Registry at <http://www.umin.ac.jp/ctr/> under number UMIN000036525 (registered 1
12
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14 107 May 2019). Approval was obtained from the Institutional Review Board of Toyonaka
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16 108 Municipal Hospital (2019-02-04). The need for informed consent will be waived via the
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18 109 *opt-out* method of each hospital website.
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6 112 **Strengths and limitations of this study**
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8 113 • The large, multicenter, nationwide dataset of radiation exposure doses for
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10 114 gastrointestinal fluoroscopic procedures in gastrointestinal endoscopy gathered in
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12 115 this study will serve as a basis for the development of diagnostic reference levels in
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15
16 116 Japan.

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18 117 • Gastrointestinal fluoroscopic procedures have been rapidly increasing in number
19
20 118 and complexity, but there are still not enough available local and national DRLs in
21
22 119 gastrointestinal endoscopy units.

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26 120 • These data may not be valid for old models of fluoroscopic systems because this
27
28 121 study will include data from fluoroscopic systems with available radiation data.
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123 INTRODUCTION

124 Medical radiation is widely used in both medical imaging and radiation treatment. In
125 medical imaging, fluoroscopy employs radiation to show a continuous X-ray image on a
126 monitor and plays a major role in the daily practices of gastroenterology, digestive
127 endoscopy, and hepatobiliary and pancreatic studies. Radiological medical imaging
128 has both benefits and drawbacks for patients. The latter is split into two types:
129 deterministic risks ¹, determined by the threshold dose, as represented by skin injury,
130 and stochastic risks, determined by a linear no-threshold model, such as the cancer
131 risk ². There have been some reports on radiation-induced skin injury in cardiology and
132 interventional radiology (IVR) ³, but reports from gastrointestinal endoscopy units are
133 rare. However, all medical staff in gastrointestinal endoscopy units need to have
134 correct knowledge of the appropriate use of medical radiation. Historically, the use of
135 medical radiation has rapidly increased since the 1990s with the spread of computed
136 tomography (CT), and the radiation-associated cancer risk was recognized in the same
137 period, even when the doses of radiation were small ^{4 5 6}. In particular, the use of CT
138 has increased approximately 12-fold in the United Kingdom and more than 20-fold in
139 the United States in the last 25 years ⁷.

140 The International Atomic Energy Agency (IAEA), the International Commission on
141 Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects
142 of Atomic Radiation (UNSCEAR), and other radiological societies have been
143 attempting to manage medical radiation exposure (RE) according to the “as low as
144 reasonably achievable” (ALARA) principle by establishing diagnostic reference levels

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6 145 (DRLs) to optimize protection from medical radiation. The concept of DRLs was first
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8 146 introduced by the ICRP 73 ⁸ in 1996. Then, the ICRP emphasized the important role of
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11 147 DRLs as a tool for optimizing patient protection ^{9 10}. Accordingly, the ICRP set specific
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14 148 target levels for various X-ray-related procedures in 2007 ⁹. This movement of setting
15
16 149 DRLs has been led by radiation-related societies in each region, although the
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19 150 movement has mainly been driven by Western countries. The ICRP 135 recommends
20
21 151 that all individuals who are involved in patient procedures with the risk of medical
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24 152 exposure should be familiar with the DRL process as a tool for optimizing protection ¹¹.
25
26 153 DRLs are now widely accepted in not only Western countries but also Japan (Japan
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29 154 DRLs 2015) ¹², and DRLs have become the global standard for all procedures that use
30
31 155 ionizing radiation. Legislation has made it mandatory to establish and record DRLs in
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34 156 Europe, but that is not the case worldwide. The introduction of DRLs in the UK
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36 157 achieved a reduction of approximately 50% in the radiation dose in typical X-ray
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39 158 examinations over 15 years ¹³. However, there is still not enough available data on RE
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41 159 for gastrointestinal fluoroscopic procedures, such as endoscopic retrograde
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44 160 cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS),
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46 161 small bowel endoscopy, and enteral stent placement; these techniques are still being
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49 162 developed and have recently been used with increasing frequency ¹⁴⁻¹⁶.
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52 163 Our gastroenterologists and endoscopists are still unfamiliar with the DRL concept.
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55 164 Among the guidelines developed by gastrointestinal endoscopy associations, the 2012
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58 165 European Gastrointestinal Endoscopy Society (ESGE) guidelines for radiation
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6 166 protection state that the entrance skin dose (ESD; approximately equivalent to air-
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8 167 kerma in this study) and kerma-area product (KAP; approximately equivalent to the
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10 168 dose-area product (DAP) in this study) during diagnostic and therapeutic ERCP are 55-
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12 169 347 mGy and 3-115/8-333 Gy cm^2 , respectively, although information regarding the
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14 170 DRLs of ERCP is limited because this statement is based on only approximately 600
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16 171 cases of ERCP in 7 reports ¹⁴. No guidelines on RE from the American Society for
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18 172 Gastrointestinal Endoscopy (ASGE) exist, but the ASGE recommends measuring and
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20 173 documenting fluoroscopy time (FT) and radiation dose in all ERCP procedures as a
21
22 174 quality indicator (level of evidence: 2C) ¹⁷. Although no guidelines for exposure have
23
24 175 been developed by the Japan Gastroenterological Endoscopy Society (JGES), a
25
26 176 description of FT exists in the item regarding ERCP in the Japan Endoscopy Database
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28 177 (JED) ¹⁸, which is scheduled to be implemented as a nationwide endoscopic survey in
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39 179 Recently, various endoscopic procedures performed under fluoroscopic guidance are
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41 180 rapidly increasing in popularity in gastrointestinal endoscopy units, where the aim is not
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43 181 only diagnosis but also therapeutic intervention. The ICRP recommends that DRLs
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45 182 should be used to manage patient doses during both diagnostic and interventional
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47 183 procedures. There is difficulty in applying the DRL concept to interventional procedures
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49 184 because the RE level depends on the complexity of the procedure and the individual
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51 185 clinical circumstances ^{10 19 20}. There have been attempts to establish DRLs for IVR
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6 186 procedures, where grouping by disease site may help minimize the wide distribution of
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8 187 RE ^{21 22}.
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12 188 The Japanese DRLs were established on a basis of a survey and released in 2015;
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14 189 these guidelines defined the DRL value for fluoroscopically guided interventional
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16 190 procedures as a fluoroscopic radiation dose rate (interventional reference point dose
17
18 191 rate) of 20 mGy/min ¹². However, it did not include information for specific procedures
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20 192 in the field of gastroenterology ¹². Therefore, we aim to prospectively collect actual RE
21
22 193 data and identify the influential factors, such as disease site, in this REX-GI study and
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24 194 to establish DRLs for the following interventional procedures in gastrointestinal
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26 195 endoscopy units: ERCP, interventional EUS, balloon-assisted enteroscopy, enteral
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28 196 metallic stent placement and enteral tube placement.
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6 197 **METHODS AND ANALYSIS**
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8 198 **Aims**
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11 199 The primary aim of this nationwide, prospective study is to collect actual data on RE
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13 200 and identify the factors affecting RE during treatments and diagnostic procedures
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16 201 under different types of fluoroscopic guidance for gastroenterology procedures,
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18 202 including the gastrointestinal, hepatobiliary and pancreatic fields, to serve as a basis
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21 203 for the establishment of DRLs in Japan.
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26 205 **Design**
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28 206 This is a multicenter, prospective observational cohort study of consecutive patients
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31 207 undergoing the following 5 treatments and diagnostic procedures under fluoroscopic
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33 208 guidance in the field of gastroenterology: 1) ERCP, 2) interventional EUS, 3) balloon-
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35 209 assisted enteroscopy, 4) enteral metallic stent placement; and 5) enteral tube
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38 210 placement. We will examine the procedure time (min), total FT (min), AK (mGy), DAP
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41 211 (Gycm²), total number of roentgenography procedures, and radiation dose rate (RDR)
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43 212 (mGy/min) during the procedures. The participating clinicians will manage patients
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46 213 according to the usual clinical practice, and the patients will undergo the above 5
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48 214 procedures. For the analysis, all data, including the related variables and outcome data
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51 215 (Tables 1 and 2), will be collected for all patients. The study (Radiation EXposure from
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53 216 GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN
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56 217 Clinical Trials Registry at <http://www.umin.ac.jp/ctr/> under the number UMIN000036525
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58 218 (registered 1 May 2019).
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9 **220 Setting**10
11 221 The study will be conducted at 7 university hospitals, 4 cancer centers, 9 general12
13 222 hospitals and 2 municipal hospitals in Japan. The participating hospitals are Toyonaka14
15 223 Municipal Hospital, Kindai University, the University of Tokyo, Fukui Prefectural16
17 224 Hospital, Kansai Rosai Hospital, Osaka City University, Ishikawa Prefectural Central18
19 225 Hospital, Tonan Hospital, Japanese Foundation for Cancer Research, Suita Municipal20
21 226 Hospital, Osaka Rosai Hospital, Osaka General Medical Center, Fukushima Medical22
23 227 University School of Medicine, Hyogo Cancer Center, Kitano Hospital, Tane General24
25 228 Hospital, Japanese Red Cross Medical Center, Kure Medical Center and Chugoku26
27 229 Cancer Center, Nagoya City University Hospital, Toho University Ohashi Medical28
29 230 Center, Osaka International Cancer Institute, and Gifu University Hospital (Figure 1).30
31 231 Table 1 shows the fluoroscopic systems and units performing procedures under32
33 232 fluoroscopic guidance in each institution. The central sites of the study are located at34
35 233 the Toyonaka Municipal Hospital and Kindai University. The participating physicians36
37 234 are gastroenterologists or endoscopists, including all experts and trainees working at38
39 235 all involved hospitals. The quality of the fluoroscopic devices will be regularly monitored40
41 236 according to the procedures in each institution.42
43 23744
45 238 **Study population**46
47 239 We will include all patients receiving usual clinical care who undergo the following48
49 240 treatments and diagnostic procedures under fluoroscopic guidance: 1) ERCP; 2)

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6 241 interventional EUS; 3) balloon-assisted enteroscopy; 4) enteral metallic stent
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8 242 placement; and 5) enteral tube placement. There is no age restriction. We will exclude
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10 243 patients who do not want to participate in this study via the *opt-out* method on each
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12 244 hospital website and patients who the attending physicians judge to be unsuitable for
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14 245 inclusion in this study.
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247 **Primary outcomes**

248 The primary outcomes will be the total FT (min), RDR (mGy/min), dose-area
249 parameters (AK (mGy) and DAP (Gycm²) and the total number of imaging studies that
250 the patients who meet the individual inclusion and exclusion criteria will undergo (Table
251 2).

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253 **Secondary outcome**

254 The secondary outcome will be the RE-related factors that affect the radiation dose in
255 each procedure. The details are shown in Table 3.

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257 **Setting the sample size**

258 According to the preliminary questionnaire survey (data not shown), the numbers of
259 examinations per year in the 8 centers that plan to participate in March 2019 are as
260 follows: 4000 ERCP procedures, 125 EUS procedures, 320 small intestine endoscopy
261 procedures, 44 esophageal stent placements, 150 gastroduodenal stent placements,
262 75 colorectal stent placements, 180 transanal ileus tube placements, and 75 ileus tube

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6 263 placements. The ICRP 135 recommends using data from 20-30 facilities to set national
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8 264 DRLs, and a survey for a particular examination in a facility should usually involve the
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11 265 collection of data from at least 20 patients ¹¹.

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13 266 To set the DRLs and to reduce intraprocedural variability in each hospital, we set the
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16 267 minimum sample size to at least 400 patients for each procedure. We believe that
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18 268 initially enrolling a high number of facilities and patients is desirable; therefore, we did
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21 269 not set an upper limit for the goals.

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25 26 271 **Data analysis plan**

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28 272 After obtaining the data, we will perform normality tests. Continuous variables will be
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31 273 expressed as medians with interquartile ranges or means with standard deviations.

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33 274 The categorical variables will be expressed as numbers in each category or as
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36 275 frequencies. To explore surrogate markers of RD, simple linear regression analysis will
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38 276 be performed to identify the relationships between procedure time, FT and RD. A
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41 277 multiple linear regression analysis will be performed to identify the factors related to
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43 278 RD. A P value of 0.05 will be considered statistically significant. All statistical analyses
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46 279 will be performed with JMP software (SAS Institute, Inc., Cary, NC, USA).

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50 51 281 **Patient and public involvement**

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53 282 Clinical factors related to ERCP and interventional EUS have been retrospectively
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56 283 collected at two sites (Toyonaka Municipal Hospital and Kindai University) ^{21 23-25} . We
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59 284 used those published data to develop plans for the design or implementation of the
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6 285 study and to determine the research question or the outcome measures. No patients
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8 286 were asked to advise us on the interpretation or writing up of results. There are no
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11 287 plans to disseminate the results of the research to study participants, but we will
12
13 288 consider disseminating the results of the research to the relevant patient community.
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18 290 **Data collection**

21 291 The clinical factors have been modified to comply with local patient flow and
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23 292 administrative requirements and have been assessed and approved by the study
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25 293 steering committee. We are collecting the password-protected case report forms by e-
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27 294 mail from each institution; these will be de-identified after all data have been collected,
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29 295 and all data queries have been addressed. A unique study identification number will
30
31 296 identify each participant and the associated clinical data. Data collection will be
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33 297 performed at 3-month intervals to prevent data loss. Data analysis will take place at the
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35 298 central study site (Kindai University). This study does not require data monitoring due
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37 299 to its nature as an observational study without interventions. Data will be retained for
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39 300 either a minimum of 5 years after the end of the study or for 10 years after publication,
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41 301 whichever is later.
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52 303 **Patient recruitment and time plan**

54 304 Patient recruitment will be carried out at the participating hospitals from May 2019 -
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57 305 December 2020.
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6 306 2021: Data analysis and writing and submission of the main manuscript for publication.
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11 308 **Ethics and dissemination**

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13 309 This observational study will be conducted in accordance with the principles of the
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16 310 Declaration of Helsinki, and approval has been obtained from the Institutional Review
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18 311 Board of Toyonaka Municipal Hospital (2019-02-04) and the institutional review board
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20
21 312 of each participating facility. The need for informed consent will be waived via the *opt-*
22
23 313 *out* method on each hospital website. The results of this study will be presented at
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26 314 gastroenterology-, endoscopy-, or radiology-related congresses and will be published
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28 315 in a peer-reviewed journal.
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36 318 **Author contributions**

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39 319 Nishida T, Hayashi S (Toyonaka Municipal Hospital), and Takenaka M (Kindai
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41
42 320 University) designed this study. Hosono M (Kindai University) critically reviewed the
43
44 321 protocol. Nishida T, Hayashi S (Toyonaka Municipal Hospital), Takenaka M (Kindai
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6 327 General Medical Center), Takagi T (Fukushima Medical University School of Medicine),
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10 329 Hospital), Ito Y (Japanese Red Cross Medical Center), Kuwai T (National Hospital
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16 332 Medical Center), Ikezawa K (Osaka International Cancer Institute), Iwashita T (Gifu
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20
21 334 participated this study and will recruit the patients. All authors accepted the final
22
23 335 version of the protocol (ver. 1.1: 2019-Mar-14, ver.1.5: 2019-July-15).
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16 352 Organization Kure Medical Center and Chugoku Cancer Center), Hiromi Kataoka,
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19
20
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22

23 355

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29
30
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37 360 **Publication and data sharing**

40 361 After completion of the study, a main manuscript will be prepared to present the results
41
42 362 and will be submitted to a clinical journal for peer review. This study will ensure that the
43
44 363 public has access to the published data. A file containing the clean dataset used for the
45
46 364 final analysis to determine the main data of the study and an explanation of the
47
48 365 variables will be made publicly accessible in an anonymized format.
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55 367 **Consent for publication**

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6 368 The principal investigators will form a publication committee, which will include key
7
8 369 members of this study, and the committee will grant authorship according to individual
9
10 370 input. Investigators who do not qualify for authorship will be acknowledged by name in
11
12 371 the final manuscript.
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21 373 **Conflicts of interest statement**
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25 374 None of the authors have any competing interests related to this research.
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6 **376 Discussion**

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9 **377** Currently, the establishment of DRLs is an international requirement for protection from
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11 **378** medical radiation. For diagnostic radiology, national and regional DRLs are usually set
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13 **379** at the 75% percentile of the distribution of a typical sample dose ²⁶. All physicians or
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16 **380** medical staff who are involved in radiological imaging or procedures under fluoroscopic
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18 **381** guidance should be familiar with the DRL process as a tool for optimizing protection. In
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20 **382** addition, separate DRLs must be established for each country and/or region because
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23 **383** the equipment and procedure protocols can vary among different regions ²⁶. However,
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26 **384** the amount of RE depends on the procedure complexity, patient anatomy, lesion
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28 **385** characteristics, disease severity ¹¹ and type of fluoroscopic devices ²¹; thus, setting the
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30 **386** upper limit of radiation use by applying uniform standards is difficult. Generally, DRLs
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33 **387** are not dose limits and do not help distinguish between good and poor medical
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36 **388** practices ²⁶. Therefore, a high demand exists for a large amount of real-world evidence.
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38
39 **389** The 2015 Japan DRLs state that the methods for establishing DRLs not only include
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41 **390** setting radiation dose levels but also includes determining the dose quantities and units
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43
44 **391** used to set the DRLs, thus standardizing the methodology for dose measurements,
45
46 **392** data collection and identification of the applications of DRLs ¹².
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49 **393** Unfortunately, most gastroenterologists are unfamiliar with not only DRLs but also
50
51 **394** radiation protection because information on RE from gastrointestinal medical treatment
52
53 **395** is currently very scarce, and few RE standards, including DRLs, have been established
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56 **396** worldwide. Given this background, the REX-GI study is planned as an observational,
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58 **397** nationwide study in Japan. Our results will help to promote radiation optimization and
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6 398 patient radiation protection in gastroenterology studies, such as digestive endoscopy,
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9 399 and hepatobiliary and pancreatic procedures.
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Table 1. Fluoroscopic system and units performing procedures under fluoroscopic guidance

	Number of Hospital Beds	Fluoroscopy Device				Fluoroscopy Unit
		Company	Device model	Apparatus type	Year of introduction	Location
Toyonaka Municipal Hospital	613	Hitachi	Exavista	Over-tube	2016	Endoscopy
Kindai University	929	Hitachi	Curevista	Over-tube	2017	Endoscopy
The University of Tokyo	1216	Hitachi	Curevista	Over-tube	2009	Radiology
		Canon Toshiba	Exavista	Over-tube	2013	
		Canon Toshiba	Ultimax-I	Under-tube	2016	
Fukui Prefectural Hospital	880	Hitachi	Versiflex	Over-tube	2008	Endoscopy
Kansai Rosai Hospital	642	Canon Toshiba	Zexira	Over-tube	2011	Radiology
		Canon Toshiba	Ultimax-I	Under-tube	2017	
Osaka City University	891	Hitachi	Curevista	Over-tube	2011	Endoscopy
		Hitachi	Versiflex vista	Under-tube	2015	Endoscopy
Ishikawa Prefectural Central Hospital	639	Canon Toshiba	Drex-zx80	Over-tube	2016	Endoscopy
Tonan Hospital	283	Hitachi	Curevista	Over-tube	2013	Radiology
		Canon Toshiba	ZEXIRA	Over-tube	2016	

Japanese Foundation for Cancer Research	686	Canon Toshiba	Ultimax-i	Under-tube	2016	Radiology
Suita Municipal Hospital	431	Hitachi	Versiflex	Under-tube	2018	Endoscopy
Osaka Rosai Hospital	678	Hitachi	Exavista	Under-tube	2018	Radiology
Osaka General Medical Center	768	Hitachi Hitachi	Curevista, Versiflex	Over-tube	2018	Endoscopy
Fukushima Medical University School of Medicine	778	Canon Toshiba Canon Toshiba	Zexira FPD1717	Over-tube	2012	Radiology
Hyogo Cancer Center	400	Hitachi	Curevista	Over-tube	2019	Endoscopy
Kitano Hospital	699	Hitachi Hitachi	Versiflex Curevista	Under-tube Over-tube	2017	Endoscopy
Tane General Hospital	304	Hitachi	Exavista	Over-tube	2011	Radiology
Japanese Red Cross Medical Center	708	Hitachi	Curevista	Over-tube	2016	Radiology
Kure Medical Center and Chugoku Cancer Center	700	Hitachi	Exavista	Over-tube	2010	Endoscopy
Nagoya City University Hospital	800	Canon Toshiba	Ultimax-I	Under-tube	2018	Endoscopy
Toho University Ohashi Medical Center	319	Canon Toshiba	Ultimax-I	Under-tube	2018	Radiology

Osaka International Cancer Institute	500	Canon Toshiba	Ultimax-I	Under-tube	2017	Endoscopy
Gifu University Hospital	606	Shimadzu	C-Vision Safire	Under-tube	2004	Radiology

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Table 2. Primary outcomes

Factors	Variables
Patients	<ul style="list-style-type: none"> ▪ Procedure type ▪ Age ▪ Sex
Fluoroscopic system	<ul style="list-style-type: none"> ▪ Fluoroscopic device (company, device model, manufacturing year) ▪ Basic use setting: frame per second (FPS), radiation field (cm²)*
Radiation exposure	<ul style="list-style-type: none"> ▪ Total fluoroscopy time (FT) (min) ▪ Air-Kerma (AK) (mGy) ▪ Dose-area product (DAP) (Gycm²) ▪ Total number of roentgenography procedures ▪ Radiation dose rate (RDR) (mGy/min)

*When the setting changes during the procedure, we will record the basic setting.

Table 3. Secondary outcomes

Procedures	Radiation exposure-related factors
ERCP	<p>(A) Surgically altered gastrointestinal anatomy Billroth I reconstruction, Billroth II reconstruction, Roux-en-Y reconstruction, pancreaticoduodenectomy</p> <p>(B) Type of endoscope</p> <p>(C) Naïve papilla</p> <p>(D) Indications for ERCP (including suspicion) are classified into the following five categories:</p> <ol style="list-style-type: none"> 1) Choledocholithiasis (maximum diameter, number of stones, presence of cholangitis, tube exchange for the above diseases, treatment for choledocholithiasis with or without balloon catheter, basket catheter, crusher, etc.) 2) Distant malignant bile duct stricture (papillary tumor, distal cholangiocarcinoma, pancreatic cancer, etc.) 3) Proximal malignant bile duct stricture (Hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, gallbladder cancer, etc.) 4) Pancreatic duct examination (pancreas cancer, intraductal papillary mucinous neoplasm, etc.) 5) Other diseases apart from those listed above (benign bile duct stricture, pancreatobiliary junction abnormality, etc.) <p>(E) Total procedure time (min) *</p>

	<p>1) Cannulation time</p> <p>2) Treatment time</p> <p>(F) Experience of the high-volume endoscopist (HVE) or low-volume endoscopist: (LVE) †</p> <p>(G) Facility scale: The number of ERCP procedures per year</p> <p>(H) Whether the fluoroscopic operator is inside or outside in the fluoroscopy room</p> <p>(I) Various treatments (endoscopic sphincterotomy, stone treatment, bile duct pancreatic stent, cytology, biopsy, naïve papilla, cannulation method, contrast agent, intubation time, first-use catheter, large balloon, crusher, drainage area or method, stent type used, cholangioscopy)</p> <p>(J) Sedation: Medication and the depth of the anesthesia ‡</p>
Interventional EUS	<p>(A) Indication for interventional EUS (EUS-guided hepaticogastrostomy (HG)), choledochoduodenostomy (CDS), cyst drainage (CD), antegrade treatment (AG), rendezvous technique (RV), pancreatic duct drainage (PD)</p> <p>(B) Total procedure time‡</p> <p> 1) Endoscope insertion time</p> <p> 2) Treatment time</p> <p>(C) Facility scale: The number of EUS interventions per year, the number of EUS-guided fine-needle aspiration (FNA) procedures per year</p> <p>(D) Double stenting (presence or absence of duodenal stenosis)</p> <p>(E) Device</p> <p>(F) Scope position</p> <p>(G) Sedation: Medication and the depth of anesthesia</p>

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<p>Balloon-assisted enteroscopy</p>	<p>(A) Disease indicating balloon-assisted enteroscopy</p> <ol style="list-style-type: none"> 1) Hemostatic or bleeding confirmation 2) Crohn's disease 3) Small intestine tumor examination 4) Others <p>(B) Insertion site: perioral or transanal</p> <p>(C) Insertion length (cm)</p> <p>(D) Total procedure time (min)</p>
<p>Enteral metallic stent placement</p>	<p>(A) Stent location</p> <ol style="list-style-type: none"> 1) Esophagus (Upper/Mid-Low/Trans) 2) Gastro-duodenum (Above pylorus/Trans pylorus /Below pylorus) 3) Colon stent (Right/Left/Rectum) <p>(B) Total procedure time (min) §</p> <ol style="list-style-type: none"> 1) Endoscope insertion time 2) Treatment time
<p>Enteral ileus tube placement</p>	<p>(A) Disease indicating ileus tube</p> <p>(B) Intranasal ileus tube insertion for ileal obstruction or transanal ileus tube insertion for malignant colonic obstruction</p> <ol style="list-style-type: none"> 1) Tube insertion length for peroral ileus tube placement (cm) 2) The occlusion site for the transanal tube (Right/Left/Rectum) <p>(D) Total procedure time (min) §</p>

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5 ERCP: endoscopic retrograde cholangiopancreatography

6 * Cannulation time is defined as the time from endoscope insertion until successful biliary cannulation, and treatment time is defined as
7 the time from successful biliary cannulation until the scope is removed from the patient. The total procedure time is defined as the time
8 from endoscope insertion until the scope is removed from the patient (cannulation time +treatment time).
9

10 ‡ Depth of anesthesia is divided into 3 levels based on the Richmond Agitation-Sedation Scale (RASS), Ramsay Scale, and Sedation-
11 Agitation Scale (SAS): good, poor, and very bad. The good level is defined as RASS score: -5 ~ -1, SAS score: 1 ~ 3, and Ramsay
12 score: 3 ~ 6 equivalent, without additional unplanned doses. The poor level is defined as RASS score: 0 ~ + 1, SAS score: 4 ~ 5, and
13 Ramsay score: 1 ~ 2, without physical restraint but with unplanned doses. The very bad level is defined as requiring physical restraint
14 with a force considered dangerous, RASS score: +2 to +4, and SAS score: 6 to 7 regardless of Ramsay score.
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16 † HVE: Endoscopists with more than 200 ERCP results and who have been involved in ERCP for over 10 years. LVE: Non-HVE
17 endoscopists who perform ERCP.
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19 ‡ Endoscope insertion time is defined as the time from endoscope insertion until the initial EUS-guided needle puncture, and treatment
20 time is defined as the time from initial EUS-guided needle puncture until the scope is removed from the patient. The total procedure
21 time is defined as the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time +treatment
22 time).
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24 ‡ Endoscope insertion time is defined as the time from endoscope insertion until initial guidewire exploration, and treatment time is
25 defined as the time from initial guidewire exploration until the scope is removed from the patient. The total procedure time is defined as
26 the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time +treatment time).
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6 **Figure legends**
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8 **Figure 1.** The participating hospitals in this study.
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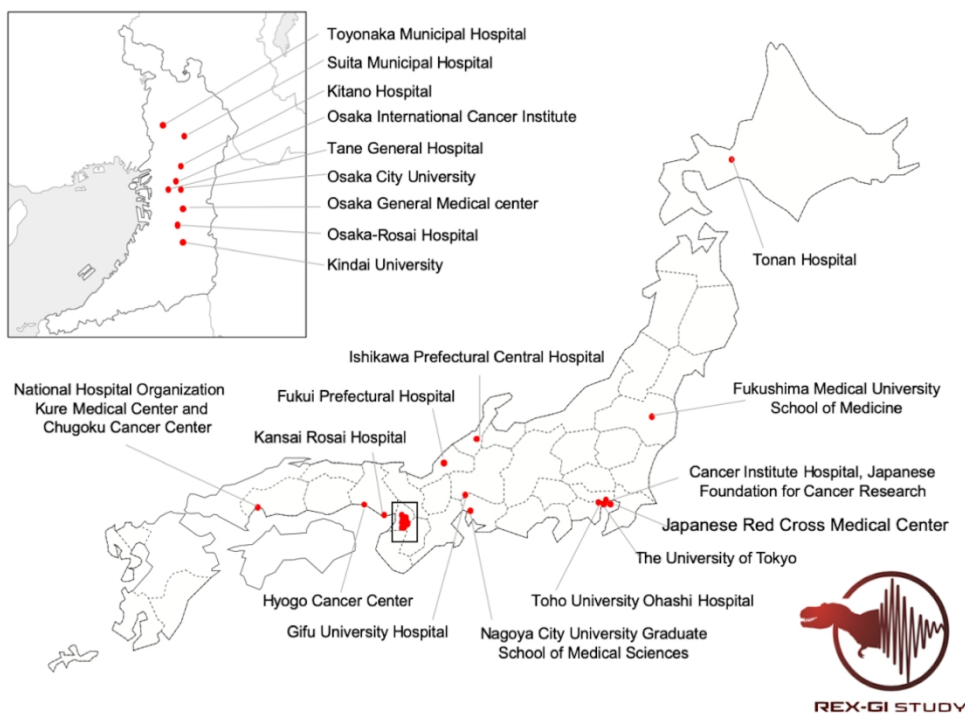


Figure 1. The participating hospitals in this study.

119x90mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6, 11
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6, 11
Protocol version	#3	Date and version identifier	16
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

1	Roles and	#5b	Name and contact information for the trial sponsor	N.A.
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	N.A.
8	responsibilities:		collection, management, analysis, and interpretation of data;	
9	sponsor and funder		writing of the report; and the decision to submit the report for	
10			publication, including whether they will have ultimate authority	
11			over any of these activities	
12				
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16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	12, 14
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for undertaking	8-10
27	rationale		the trial, including summary of relevant studies (published and	
28			unpublished) examining benefits and harms for each intervention	
29				
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32	Background and	#6b	Explanation for choice of comparators	9
33	rationale: choice of			
34	comparators			
35				
36				
37	Objectives	#7	Specific objectives or hypotheses	9-10
38				
39				
40	Trial design	#8	Description of trial design including type of trial (eg, parallel	11
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
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46	Methods:			
47	Participants,			
48	interventions, and			
49	outcomes			
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53	Study setting	#9	Description of study settings (eg, community clinic, academic	12
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
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1 2 3 4 5	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
6 7 8 9	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N.A.
10 11 12 13 14	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N.A.
15 16 17 18 19	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N.A.
20 21 22 23	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N.A.
24 25 26 27 28 29 30 31 32 33	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
34 35 36 37 38	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15
39 40 41 42 43 44	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
45 46 47 48	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
49 50 51 52 53	Methods: Assignment of interventions (for controlled trials)			
54 55 56 57 58 59	Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	N.A.

provided in a separate document that is unavailable to those who enrol participants or assign interventions

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4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central N.A.
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
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11	Allocation:	#16c	Who will generate the allocation sequence, who will enrol N.A.
12	implementation		participants, and who will assign participants to interventions
13			
14	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial N.A.
15			participants, care providers, outcome assessors, data analysts),
16			and how
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20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, N.A.
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
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25	Methods: Data		
26	collection,		
27	management, and		
28	analysis		
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32	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and 14
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
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43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, 15
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48	Data management	#19	Plans for data entry, coding, security, and storage, including any 15
49			related processes to promote data quality (eg, double data entry;
50			range checks for data values). Reference to where details of data
51			management procedures can be found, if not in the protocol
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55	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary 14
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
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1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	N.A.
2	analyses		analyses)	
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	15
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
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10	Methods: Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	15
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
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22	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	15
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
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27	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	N.A.
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
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33	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	N.A.
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
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38	Ethics and			
39	dissemination			
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42	Research ethics	#24	Plans for seeking research ethics committee / institutional review	15
43	approval		board (REC / IRB) approval	
44				
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46	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	N.A.
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
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53	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	15
54			participants or authorised surrogates, and how (see Item 32)	
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1	Consent or assent:	#26b	Additional consent provisions for collection and use of	N.A.
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
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6	Confidentiality	#27	How personal information about potential and enrolled	14
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
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11	Declaration of interests	#28	Financial and other competing interests for principal investigators	17, 18
12			for the overall trial and each study site	
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15	Data access	#29	Statement of who will have access to the final trial dataset, and	17
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
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20	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	N.A.
21	care		compensation to those who suffer harm from trial participation	
22				
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24	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results	14
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
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33	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	18
34	authorship		professional writers	
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37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	N.A.
38	reproducible research		participant-level dataset, and statistical code	
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41	Appendices			
42				
43	Informed consent	#32	Model consent form and other related documentation given to	N.A.
44	materials		participants and authorised surrogates	
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47	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N.A.
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
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BMJ Open

A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-033604.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Dec-2019
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	Maetani, Iruru ; Toho University Ohashi Medical Center, Division of Gastroenterology and Hepatology, Department of Internal Medicine Ikezawa, Kenji ; Osaka International Cancer Institute, Department of Hepatobiliary and Pancreatic Oncology Iwashita, Takuji ; Gifu University Hospital, First Department of Internal Medicine Matsumoto, Kengo; Toyonaka Municipal Hospital, Department of Gastroenterology Inada, Masami ; Toyonaka Municipal Hospital, Department of Gastroenterology
Primary Subject Heading :	Gastroenterology and hepatology
Secondary Subject Heading :	Radiology and imaging, Public health, Research methods
Keywords :	Radiation Exposure, Diagnostic Reference Levels, ERCP, Gastrointestinal Fluoroscopic Procedure, Endoscopy < GASTROENTEROLOGY

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1 **A Multicenter Prospective Observational Study Protocol for Radiation Exposure**
2 **from Gastrointestinal Fluoroscopic Procedures (REX-GI study)**

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43 80 Fluoroscopic Procedure, Endoscopy.
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6 **82 ABSTRACT**

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8 **83 INTRODUCTION:** Recently, the use of various endoscopic procedures under X-ray
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11 **84** fluoroscopic guidance, such as endoscopic retrograde cholangiopancreatography
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13 **85** (ERCP), interventional endoscopic ultrasonography (EUS), enteral endoscopy, and
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16 **86** stenting, has been rapidly increasing because of the minimally invasive nature of these
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18 **87** procedures compared to that of surgical intervention. With the spread of computed
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21 **88** tomography and fluoroscopic interventions, including endoscopic procedures under X-
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24 **89** ray guidance, high levels of radiation exposure (RE) from medical imaging have led to
25
26 **90** major concerns throughout society. However, information about RE related to these
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28 **91** image-guided procedures in gastrointestinal endoscopy is scarce, and the RE
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31 **92** reference levels have not been established. The aim of this study is to prospectively
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34 **93** collect the actual RE dose and to help establish diagnostic reference levels (DRLs) in
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36 **94** the field of gastroenterology in Japan.

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38 **95 METHODS AND ANALYSIS:** This study is a multicenter, prospective observational
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41 **96** study that is being conducted to collect the actual RE from treatments and diagnostic
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44 **97** procedures, including ERCP, interventional EUS, balloon-assisted enteroscopy, enteral
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46 **98** metallic stent placement and enteral tube placement. We will measure the total
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48 **99** fluoroscopy time (FT, min), the total dose-area product (DAP, Gy cm^2) and air-kerma
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51 **100** (AK, mGy) of those procedures. Because we are collecting the actual RE data and
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54 **101** identifying the influential factors through a prospective, nationwide design, this study
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56 **102** will provided guidance regarding the DRLs of ERCP, interventional EUS, balloon-
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58 **103** assisted enteroscopy, enteral metallic stent placement and enteral tube placement.
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6 104 **ETHICS AND DISSEMINATION:** This trial (Radiation EXposure from GastroIntestinal
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9 105 fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials
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11 106 Registry at <http://www.umin.ac.jp/ctr/> under number UMIN000036525 (registered 1
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14 107 May 2019). Approval was obtained from the Institutional Review Board of Toyonaka
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16 108 Municipal Hospital (2019-02-04). The need for informed consent will be waived via the
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18 109 *opt-out* method of each hospital website.
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6 112 **Strengths and limitations of this study**
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8 113 • The large, multicenter, nationwide dataset of radiation exposure doses for
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10 114 gastrointestinal fluoroscopic procedures in gastrointestinal endoscopy gathered in
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12 115 this study will serve as a basis for the development of diagnostic reference levels in
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16 116 Japan.

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18 117 • Gastrointestinal fluoroscopic procedures have been rapidly increasing in number
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20 118 and complexity, but there are still not enough available local and national DRLs in
21
22 119 gastrointestinal endoscopy units.

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26 120 • These data may not be valid for old models of fluoroscopic systems because this
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28 121 study will include data from fluoroscopic systems with available radiation data.
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123 INTRODUCTION

124 Medical radiation is widely used in both medical imaging and radiation treatment. In
125 medical imaging, fluoroscopy employs radiation to show a continuous X-ray image on a
126 monitor and plays a major role in the daily practices of gastroenterology, digestive
127 endoscopy, and hepatobiliary and pancreatic studies. Radiological medical imaging
128 has both benefits and drawbacks for patients. The latter is split into two types:
129 deterministic risks ¹, determined by the threshold dose, as represented by skin injury,
130 and stochastic risks, determined by a linear no-threshold model, such as the cancer
131 risk ². There have been some reports on radiation-induced skin injury in cardiology and
132 interventional radiology (IVR) ³, but reports from gastrointestinal endoscopy units are
133 rare. However, all medical staff in gastrointestinal endoscopy units need to have
134 correct knowledge of the appropriate use of medical radiation. Historically, the use of
135 medical radiation has rapidly increased since the 1990s with the spread of computed
136 tomography (CT), and the radiation-associated cancer risk was recognized in the same
137 period, even when the doses of radiation were small ^{4 5 6}. In particular, the use of CT
138 has increased approximately 12-fold in the United Kingdom and more than 20-fold in
139 the United States in the last 25 years ⁷.

140 The International Atomic Energy Agency (IAEA), the International Commission on
141 Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects
142 of Atomic Radiation (UNSCEAR), and other radiological societies have been
143 attempting to manage medical radiation exposure (RE) according to the “as low as
144 reasonably achievable” (ALARA) principle by establishing diagnostic reference levels

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6 145 (DRLs) to optimize protection from medical radiation. The concept of DRLs was first
7
8 146 introduced by the ICRP 73 ⁸ in 1996. Then, the ICRP emphasized the important role of
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11 147 DRLs as a tool for optimizing patient protection ^{9 10}. Accordingly, the ICRP set specific
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13 148 target levels for various X-ray-related procedures in 2007 ⁹. This movement of setting
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16 149 DRLs has been led by radiation-related societies in each region, although the
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18 150 movement has mainly been driven by Western countries. The ICRP 135 recommends
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21 151 that all individuals who are involved in patient procedures with the risk of medical
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23 152 exposure should be familiar with the DRL process as a tool for optimizing protection ¹¹.
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26 153 DRLs are now widely accepted in not only Western countries but also Japan (Japan
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28 154 DRLs 2015) ¹², and DRLs have become the global standard for all procedures that use
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31 155 ionizing radiation. Legislation has made it mandatory to establish and record DRLs in
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33 156 Europe, but that is not the case worldwide. The introduction of DRLs in the UK
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36 157 achieved a reduction of approximately 50% in the radiation dose in typical X-ray
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38 158 examinations over 15 years ¹³. However, there is still not enough available data on RE
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41 159 for gastrointestinal fluoroscopic procedures, such as endoscopic retrograde
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43 160 cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS),
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46 161 small bowel endoscopy, and enteral stent placement; these techniques are still being
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48 162 developed and have recently been used with increasing frequency ^{14 15}.
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52 163 Our gastroenterologists and endoscopists are still unfamiliar with the DRL concept.
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54 164 Among the guidelines developed by gastrointestinal endoscopy associations, the 2012
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57 165 European Gastrointestinal Endoscopy Society (ESGE) guidelines for radiation
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6 166 protection state that the entrance skin dose (ESD; approximately equivalent to air-
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9 167 kerma in this study) and kerma-area product (KAP; approximately equivalent to the
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11 168 dose-area product (DAP) in this study) during diagnostic and therapeutic ERCP are 55-
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14 169 347 mGy and 3-115/8-333 Gy cm^2 , respectively, although information regarding the
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16 170 DRLs of ERCP is limited because this statement is based on only approximately 600
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18 171 cases of ERCP in 7 reports ¹⁴. No guidelines on RE from the American Society for
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21 172 Gastrointestinal Endoscopy (ASGE) exist, but the ASGE recommends measuring and
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23 173 documenting fluoroscopy time (FT) and radiation dose in all ERCP procedures as a
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25 174 quality indicator (level of evidence: 2C) ¹⁶. Although no guidelines for exposure have
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28 175 been developed by the Japan Gastroenterological Endoscopy Society (JGES), a
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31 176 description of FT exists in the item regarding ERCP in the Japan Endoscopy Database
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33 177 (JED) ¹⁷, which is scheduled to be implemented as a nationwide endoscopic survey in
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36 178 2020.

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39 179 Recently, various endoscopic procedures performed under fluoroscopic guidance are
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42 180 rapidly increasing in popularity in gastrointestinal endoscopy units, where the aim is not
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45 181 only diagnosis but also therapeutic intervention. The ICRP recommends that DRLs
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47 182 should be used to manage patient doses during both diagnostic and interventional
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50 183 procedures. There is difficulty in applying the DRL concept to interventional procedures
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52 184 because the RE level depends on the complexity of the procedure and the individual
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55 185 clinical circumstances ^{10 18 19}. There have been attempts to establish DRLs for IVR
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6 186 procedures, where grouping by disease site may help minimize the wide distribution of
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8 187 RE^{20 21}.
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12 188 The Japanese DRLs were established on a basis of a survey and released in 2015;
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14 189 these guidelines defined the DRL value for fluoroscopically guided interventional
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16 190 procedures as a fluoroscopic radiation dose rate (interventional reference point dose
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18 191 rate) of 20 mGy/min¹². However, it did not include information for specific procedures
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20 192 in the field of gastroenterology¹². Therefore, we aim to prospectively collect actual RE
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22 193 data and identify the influential factors, such as disease site, in this REX-GI study and
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24 194 to establish DRLs for the following interventional procedures in gastrointestinal
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26 195 endoscopy units: ERCP, interventional EUS, balloon-assisted enteroscopy, enteral
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28 196 metallic stent placement and enteral tube placement.
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6 197 **METHODS AND ANALYSIS**
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8 198 **Aims**
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11 199 The primary aim of this nationwide, prospective study is to collect actual data on RE
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13 200 and identify the factors affecting RE during treatments and diagnostic procedures
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16 201 under different types of fluoroscopic guidance for gastroenterology procedures,
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18 202 including the gastrointestinal, hepatobiliary and pancreatic fields, to serve as a basis
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21 203 for the establishment of DRLs in Japan.
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26 205 **Design**
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28 206 This is a multicenter, prospective observational cohort study of consecutive patients
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31 207 undergoing the following 5 treatments and diagnostic procedures under fluoroscopic
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33 208 guidance in the field of gastroenterology: 1) ERCP, 2) interventional EUS, 3) balloon-
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35 209 assisted enteroscopy, 4) enteral metallic stent placement; and 5) enteral tube
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38 210 placement. We will examine the procedure time (min), total FT (min), AK (mGy), DAP
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41 211 (Gycm²), total number of roentgenography procedures, and radiation dose rate (RDR)
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43 212 (mGy/min) during the procedures. The participating clinicians will manage patients
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46 213 according to the usual clinical practice, and the patients will undergo the above 5
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48 214 procedures. For the analysis, all data, including the related variables and outcome data
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51 215 (Tables 1 and 2), will be collected for all patients. The study (Radiation EXposure from
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53 216 GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN
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56 217 Clinical Trials Registry at <http://www.umin.ac.jp/ctr/> under the number UMIN000036525
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58 218 (registered 1 May 2019).
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220 Setting

221 The study will be conducted at 7 university hospitals, 4 cancer centers, 9 general
222 hospitals and 2 municipal hospitals in Japan. The participating hospitals are Toyonaka
223 Municipal Hospital, Kindai University, the University of Tokyo, Fukui Prefectural
224 Hospital, Kansai Rosai Hospital, Osaka City University, Ishikawa Prefectural Central
225 Hospital, Tonan Hospital, Japanese Foundation for Cancer Research, Suita Municipal
226 Hospital, Osaka Rosai Hospital, Osaka General Medical Center, Fukushima Medical
227 University School of Medicine, Hyogo Cancer Center, Kitano Hospital, Tane General
228 Hospital, Japanese Red Cross Medical Center, Kure Medical Center and Chugoku
229 Cancer Center, Nagoya City University Hospital, Toho University Ohashi Medical
230 Center, Osaka International Cancer Institute, and Gifu University Hospital (Figure 1).
231 Table 1 shows the fluoroscopic systems and units performing procedures under
232 fluoroscopic guidance in each institution. The central sites of the study are located at
233 the Toyonaka Municipal Hospital and Kindai University. The participating physicians
234 are gastroenterologists or endoscopists, including all experts and trainees working at
235 all involved hospitals. The quality of the fluoroscopic devices will be regularly monitored
236 according to the procedures in each institution.

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238 Study population

239 We will include all patients receiving usual clinical care who undergo the following
240 treatments and diagnostic procedures under fluoroscopic guidance: 1) ERCP; 2)

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6 241 interventional EUS; 3) balloon-assisted enteroscopy; 4) enteral metallic stent
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8 242 placement; and 5) enteral tube placement. There is no age restriction. We will exclude
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10 243 patients who do not want to participate in this study via the *opt-out* method on each
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12 244 hospital website and patients who the attending physicians judge to be unsuitable for
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14 245 inclusion in this study.
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247 **Primary outcomes**

248 The primary outcomes will be the total FT (min), RDR (mGy/min), dose-area
249 parameters (AK (mGy) and DAP (Gycm²) and the total number of imaging studies that
250 the patients who meet the individual inclusion and exclusion criteria will undergo (Table
251 2).

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253 **Secondary outcome**

254 The secondary outcome will be the RE-related factors that affect the radiation dose in
255 each procedure. The details are shown in Table 3.

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257 **Setting the sample size**

258 According to the preliminary questionnaire survey (data not shown), the numbers of
259 examinations per year in the 8 centers that plan to participate in March 2019 are as
260 follows: 4000 ERCP procedures, 125 EUS procedures, 320 small intestine endoscopy
261 procedures, 44 esophageal stent placements, 150 gastroduodenal stent placements,
262 75 colorectal stent placements, 180 transanal ileus tube placements, and 75 ileus tube

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6 263 placements. The ICRP 135 recommends using data from 20-30 facilities to set national
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8 264 DRLs, and a survey for a particular examination in a facility should usually involve the
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11 265 collection of data from at least 20 patients ¹¹.

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13 266 To set the DRLs and to reduce intraprocedural variability in each hospital, we set the
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16 267 minimum sample size to at least 400 patients for each procedure. We believe that
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18 268 initially enrolling a high number of facilities and patients is desirable; therefore, we did
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21 269 not set an upper limit for the goals.

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25 26 271 **Data analysis plan**

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28 272 After obtaining the data, we will perform normality tests. Continuous variables will be
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31 273 expressed as medians with interquartile ranges or means with standard deviations.

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33 274 The categorical variables will be expressed as numbers in each category or as
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36 275 frequencies. To explore surrogate markers of RD, simple linear regression analysis will
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38 276 be performed to identify the relationships between procedure time, FT and RD. A
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41 277 multiple linear regression analysis will be performed to identify the factors related to
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43 278 RD. A P value of 0.05 will be considered statistically significant. All statistical analyses
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46 279 will be performed with JMP software (SAS Institute, Inc., Cary, NC, USA).

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50 51 281 **Patient and public involvement**

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53 282 Clinical factors related to ERCP and interventional EUS have been retrospectively
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56 283 collected at two sites (Toyonaka Municipal Hospital and Kindai University) ^{20 22-24} . We
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59 284 used those published data to develop plans for the design or implementation of the
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6 285 study and to determine the research question or the outcome measures. No patients
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8 286 were asked to advise us on the interpretation or writing up of results. There are no
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11 287 plans to disseminate the results of the research to study participants, but we will
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13 288 consider disseminating the results of the research to the relevant patient community.
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18 290 **Data collection**

21 291 The clinical factors have been modified to comply with local patient flow and
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23 292 administrative requirements and have been assessed and approved by the study
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25 293 steering committee. We are collecting the password-protected case report forms by e-
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27 294 mail from each institution; these will be de-identified after all data have been collected,
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29 295 and all data queries have been addressed. A unique study identification number will
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31 296 identify each participant and the associated clinical data. Data collection will be
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33 297 performed at 3-month intervals to prevent data loss. Data analysis will take place at the
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35 298 central study site (Kindai University). This study does not require data monitoring due
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37 299 to its nature as an observational study without interventions. Data will be retained for
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39 300 either a minimum of 5 years after the end of the study or for 10 years after publication,
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41 301 whichever is later.
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52 303 **Patient recruitment and schedule**

54 304 Patient recruitment will be carried out at the participating hospitals from May 2019 -
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56 305 December 2020.
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6 306 2021: Data analysis and writing and submission of the main manuscript for publication.
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11 308 **Ethics and dissemination**

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13 309 This observational study will be conducted in accordance with the principles of the

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16 310 Declaration of Helsinki, and approval has been obtained from the Institutional Review

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18 311 Board of Toyonaka Municipal Hospital (2019-02-04) and the institutional review board

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20 312 of each participating facility. The need for informed consent will be waived via the *opt-*

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22 313 *out* method on each hospital website. The results of this study will be presented at

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24 314 gastroenterology-, endoscopy-, or radiology-related congresses and will be published

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26 315 in a peer-reviewed journal.
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33 317 **Discussion**

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35 318 Currently, the establishment of DRLs is an international requirement for protection from

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37 319 medical radiation. For diagnostic radiology, national and regional DRLs are usually set

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39 320 at the 75% percentile of the distribution of a typical sample dose ²⁵. All physicians or

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41 321 medical staff who are involved in radiological imaging or procedures under fluoroscopic

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43 322 guidance should be familiar with the DRL process as a tool for optimizing protection. In

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45 323 addition, separate DRLs must be established for each country and/or region because

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47 324 the equipment and procedure protocols can vary among different regions ²⁵. However,

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49 325 the amount of RE depends on the procedure complexity, patient anatomy, lesion

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51 326 characteristics, disease severity ¹¹ and type of fluoroscopic devices ²⁰; thus, setting the

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53 327 upper limit of radiation use by applying uniform standards is difficult. Generally, DRLs
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6 328 are not dose limits and do not help distinguish between good and poor medical
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8 329 practices ²⁵. Therefore, a high demand exists for a large amount of real-world evidence.
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10 330 The 2015 Japan DRLs state that the methods for establishing DRLs not only include
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12 331 setting radiation dose levels but also includes determining the dose quantities and units
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14 332 used to set the DRLs, thus standardizing the methodology for dose measurements,
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16 333 data collection and identification of the applications of DRLs ¹².
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18 334 Unfortunately, most gastroenterologists are unfamiliar with not only DRLs but also
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20 335 radiation protection because information on RE from gastrointestinal medical treatment
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22 336 is currently very scarce, and few RE standards, including DRLs, have been established
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24 337 worldwide. Given this background, the REX-GI study is planned as an observational,
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26 338 nationwide study in Japan. Our results will help to promote radiation optimization and
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28 339 patient radiation protection in gastroenterology studies, such as digestive endoscopy,
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30 340 and hepatobiliary and pancreatic procedures.
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343 **Author contributions**

344 Nishida T, Hayashi S (Toyonaka Municipal Hospital), and Takenaka M (Kindai
345 University) designed this study. Hosono M (Kindai University) critically reviewed the
346 protocol. Nishida T, Hayashi S (Toyonaka Municipal Hospital), Takenaka M (Kindai
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27 358 University Hospital), Matsumoto K, and Inada M (Toyonaka Municipal Hospital)
28
29 359 participated this study and will recruit the patients. All authors accepted the final
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33 360 version of the protocol (ver. 1.1: 2019-Mar-14, ver.1.5: 2019-July-15).
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13 373 Cancer Research), Takumi Kanagawa, Yuichi Yoshida, Masafumi Naito (Suita
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18 375 (Fukushima Medical University School of Medicine), Naoki Fujimoto (Tane General
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20 376 Hospital), Ikuya Miki (Hyogo Cancer Center), Yuzuru Tamaru (National Hospital
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44 385 **Publication and data sharing**

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47 386 After completion of the study, a main manuscript will be prepared to present the results
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49 387 and will be submitted to a clinical journal for peer review. This study will ensure that the
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51 388 public has access to the published data. A file containing the clean dataset used for the
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53 389 final analysis to determine the main data of the study and an explanation of the
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55 390 variables will be made publicly accessible in an anonymized format.
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8 392 **Consent for publication**

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11 393 The principal investigators will form a publication committee, which will include key
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13 394 members of this study, and the committee will grant authorship according to individual
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16 395 input. Investigators who do not qualify for authorship will be acknowledged by name in
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18 396 the final manuscript.

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26 398 **Conflicts of interest statement**

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30 399 None of the authors have any competing interests related to this research.

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Table 1. Fluoroscopic system and units performing procedures under fluoroscopic guidance

	Number of Hospital Beds	Fluoroscopy Device				Fluoroscopy Unit
		Company	Device model	Apparatus type	Year of introduction	Location
Toyonaka Municipal Hospital	613	Hitachi	Exavista	Over-tube	2016	Endoscopy
Kindai University	929	Hitachi	Curevista	Over-tube	2017	Endoscopy
The University of Tokyo	1216	Hitachi	Curevista	Over-tube	2009	Radiology
		Canon Toshiba	Exavista	Over-tube	2013	
		Canon Toshiba	Ultimax-I	Under-tube	2016	
Fukui Prefectural Hospital	880	Hitachi	Versiflex	Over-tube	2008	Endoscopy
Kansai Rosai Hospital	642	Canon Toshiba	Zexira	Over-tube	2011	Radiology
		Canon Toshiba	Ultimax-I	Under-tube	2017	
Osaka City University	891	Hitachi	Curevista	Over-tube	2011	Endoscopy
		Hitachi	Versiflex Vista	Under-tube	2015	Endoscopy
Ishikawa Prefectural Central Hospital	639	Canon Toshiba	Drex-zx80	Over-tube	2016	Endoscopy
Tonan Hospital	283	Hitachi	Curevista	Over-tube	2013	Radiology
		Canon Toshiba	ZEXIRA	Over-tube	2016	

Japanese Foundation for Cancer Research	686	Canon Toshiba	Ultimax-i	Under-tube	2016	Radiology
Suita Municipal Hospital	431	Hitachi	Versiflex	Under-tube	2018	Endoscopy
Osaka Rosai Hospital	678	Hitachi	Exavista	Under-tube	2018	Radiology
Osaka General Medical Center	768	Hitachi Hitachi	Curevista, Versiflex	Over-tube	2018	Endoscopy
Fukushima Medical University School of Medicine	778	Canon Toshiba Canon Toshiba	Zexira FPD1717	Over-tube	2012	Radiology
Hyogo Cancer Center	400	Hitachi	Curevista	Over-tube	2019	Endoscopy
Kitano Hospital	699	Hitachi Hitachi	Versiflex Curevista	Under-tube Over-tube	2017	Endoscopy
Tane General Hospital	304	Hitachi	Exavista	Over-tube	2011	Radiology
Japanese Red Cross Medical Center	708	Hitachi	Curevista	Over-tube	2016	Radiology
Kure Medical Center and Chugoku Cancer Center	700	Hitachi	Exavista	Over-tube	2010	Endoscopy
Nagoya City University Hospital	800	Canon Toshiba	Ultimax-I	Under-tube	2018	Endoscopy
Toho University Ohashi Medical Center	319	Canon Toshiba	Ultimax-I	Under-tube	2018	Radiology

Osaka International Cancer Institute	500	Canon Toshiba	Ultimax-I	Under-tube	2017	Endoscopy
Gifu University Hospital	606	Shimadzu	C-Vision Safire	Under-tube	2004	Radiology

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Table 2. Primary outcomes

Factors	Variables
Patients*	<ul style="list-style-type: none"> ▪ Procedure type ▪ Age ▪ Sex
Fluoroscopic system	<ul style="list-style-type: none"> ▪ Fluoroscopic device (company, device model, manufacturing year) ▪ Basic use setting: frame per second (FPS), radiation field (cm²) ‡
Radiation exposure	<ul style="list-style-type: none"> ▪ Total fluoroscopy time (FT) (min) ▪ Air-Kerma (AK) (mGy) ▪ Dose-area product (DAP) (Gycm²) ▪ Total number of roentgenography procedures ▪ Radiation dose rate (RDR) (mGy/min)

* We will not collect patient weight or height because we will have selected patients of standard size for the Japanese population, whose weight will range from 50 to 70 kg.

‡ When the setting changes during the procedure, we will record the basic setting.

Table 3. Secondary outcomes

Procedures	Radiation exposure-related factors
ERCP	<p>(A) Surgically altered gastrointestinal anatomy Billroth I reconstruction, Billroth II reconstruction, Roux-en-Y reconstruction, pancreaticoduodenectomy</p> <p>(B) Type of endoscope</p> <p>(C) Naïve papilla</p> <p>(D) Indications for ERCP (including suspicion) are classified into the following five categories:</p> <ol style="list-style-type: none"> 1) Choledocholithiasis (maximum diameter, number of stones, presence of cholangitis, tube exchange for the above diseases, treatment for choledocholithiasis with or without balloon catheter, basket catheter, crusher, etc.) 2) Distant malignant bile duct stricture (papillary tumor, distal cholangiocarcinoma, pancreatic cancer, etc.) 3) Proximal malignant bile duct stricture (Hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, gallbladder cancer, etc.) 4) Pancreatic duct examination (pancreas cancer, intraductal papillary mucinous neoplasm, etc.) 5) Other diseases apart from those listed above (benign bile duct stricture, pancreatobiliary junction abnormality, etc.) <p>(E) Total procedure time (min) *</p>

	<p>1) Cannulation time</p> <p>2) Treatment time</p> <p>(F) Experience of the high-volume endoscopist (HVE) or low-volume endoscopist: (LVE) †</p> <p>(G) Facility scale: The number of ERCP procedures per year</p> <p>(H) Whether the fluoroscopic operator is inside or outside in the fluoroscopy room</p> <p>(I) Various treatments (endoscopic sphincterotomy, stone treatment, bile duct pancreatic stent, cytology, biopsy, naïve papilla, cannulation method, contrast agent, intubation time, first-use catheter, large balloon, crusher, drainage area or method, stent type used, cholangioscopy)</p> <p>(J) Sedation: Medication and the depth of the anesthesia ‡</p>
Interventional EUS	<p>(A) Indication for interventional EUS (EUS-guided hepaticogastrostomy (HG)), choledochoduodenostomy (CDS), cyst drainage (CD), antegrade treatment (AG), rendezvous technique (RV), pancreatic duct drainage (PD)</p> <p>(B) Total procedure time‡</p> <p>1) Endoscope insertion time</p> <p>2) Treatment time</p> <p>(C) Facility scale: The number of EUS interventions per year, the number of EUS-guided fine-needle aspiration (FNA) procedures per year</p> <p>(D) Double stenting (presence or absence of duodenal stenosis)</p> <p>(E) Device</p> <p>(F) Scope position</p> <p>(G) Sedation: Medication and the depth of anesthesia</p>

Balloon-assisted enteroscopy	<p>(A) Disease indicating balloon-assisted enteroscopy</p> <ol style="list-style-type: none"> 1) Hemostatic or bleeding confirmation 2) Crohn's disease 3) Small intestine tumor examination 4) Others <p>(B) Insertion site: perioral or transanal</p> <p>(C) Insertion length (cm)</p> <p>(D) Total procedure time (min)</p>
Enteral metallic stent placement	<p>(A) Stent location</p> <ol style="list-style-type: none"> 1) Esophagus (Upper/Mid-Low/Trans) 2) Gastro-duodenum (Above pylorus/Trans pylorus /Below pylorus) 3) Colon stent (Right/Left/Rectum) <p>(B) Total procedure time (min) §</p> <ol style="list-style-type: none"> 1) Endoscope insertion time 2) Treatment time
Enteral ileus tube placement	<p>(A) Disease indicating ileus tube</p> <p>(B) Intranasal ileus tube insertion for ileal obstruction or transanal ileus tube insertion for malignant colonic obstruction</p> <ol style="list-style-type: none"> 1) Tube insertion length for peroral ileus tube placement (cm) 2) The occlusion site for the transanal tube (Right/Left/Rectum) <p>(D) Total procedure time (min) §</p>

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5 ERCP: endoscopic retrograde cholangiopancreatography

6 * Cannulation time is defined as the time from endoscope insertion until successful biliary cannulation, and treatment time is defined as
7 the time from successful biliary cannulation until the scope is removed from the patient. The total procedure time is defined as the time
8 from endoscope insertion until the scope is removed from the patient (cannulation time + treatment time).

9 ‡ Depth of anesthesia is divided into 3 levels based on the Richmond Agitation-Sedation Scale (RASS), Ramsay Scale, and Sedation-
10 Agitation Scale (SAS): good, poor, and very bad. The good level is defined as RASS score: -5 ~ -1, SAS score: 1 ~ 3, and Ramsay
11 score: 3 ~ 6 equivalent, without additional unplanned doses. The poor level is defined as RASS score: 0 ~ +1, SAS score: 4 ~ 5, and
12 Ramsay score: 1 ~ 2, without physical restraint but with unplanned doses. The very bad level is defined as requiring physical restraint
13 with a force considered dangerous, RASS score: +2 to +4, and SAS score: 6 to 7 regardless of Ramsay score.

14 † HVE: Endoscopists with more than 200 ERCP results and who have been involved in ERCP for over 10 years. LVE: Non-HVE
15 endoscopists who perform ERCP.

16 ‡ Endoscope insertion time is defined as the time from endoscope insertion until the initial EUS-guided needle puncture, and treatment
17 time is defined as the time from initial EUS-guided needle puncture until the scope is removed from the patient. The total procedure
18 time is defined as the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time + treatment
19 time).

20 ‡ Endoscope insertion time is defined as the time from endoscope insertion until initial guidewire exploration, and treatment time is
21 defined as the time from initial guidewire exploration until the scope is removed from the patient. The total procedure time is defined as
22 the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time + treatment time).

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6 **Figure legends**
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8 **Figure 1.** The participating hospitals in this study.
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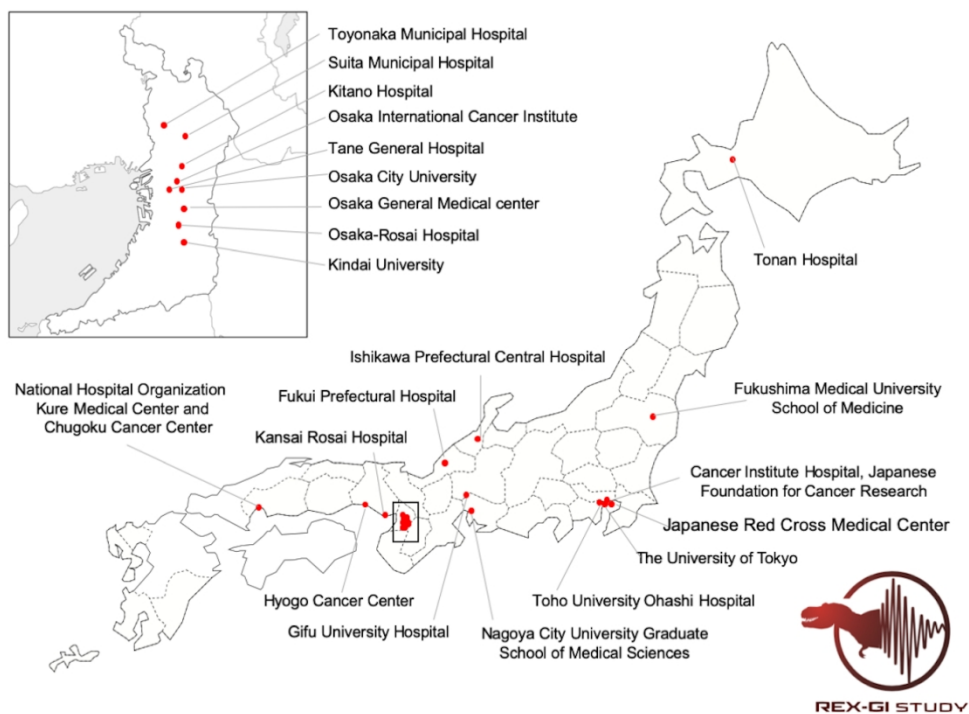


Figure 1. The participating hospitals in this study.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6, 11
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6, 11
Protocol version	#3	Date and version identifier	16
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

1	Roles and	#5b	Name and contact information for the trial sponsor	N.A.
2	responsibilities:			
3	sponsor contact			
4	information			
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7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	N.A.
8	responsibilities:		collection, management, analysis, and interpretation of data;	
9	sponsor and funder		writing of the report; and the decision to submit the report for	
10			publication, including whether they will have ultimate authority	
11			over any of these activities	
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16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	12, 14
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for undertaking	8-10
27	rationale		the trial, including summary of relevant studies (published and	
28			unpublished) examining benefits and harms for each intervention	
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32	Background and	#6b	Explanation for choice of comparators	9
33	rationale: choice of			
34	comparators			
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37	Objectives	#7	Specific objectives or hypotheses	9-10
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40	Trial design	#8	Description of trial design including type of trial (eg, parallel	11
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
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46	Methods:			
47	Participants,			
48	interventions, and			
49	outcomes			
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53	Study setting	#9	Description of study settings (eg, community clinic, academic	12
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N.A.
7	description			
8				
9				
10	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N.A.
11	modifications			
12				
13				
14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N.A.
16	adherence			
17				
18				
19				
20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N.A.
21	concomitant care			
22				
23				
24	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
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34	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15
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40	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
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45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
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49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	N.A.
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
9			
10			
11	Allocation:	#16c	Who will generate the allocation sequence, who will enrol
12	implementation		participants, and who will assign participants to interventions
13			
14			
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial
16			participants, care providers, outcome assessors, data analysts),
17			and how
18			
19			
20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
23			
24			
25	Methods: Data		
26	collection,		
27	management, and		
28	analysis		
29			
30			
31			
32	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
39			
40			
41			
42			
43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48			
49	Data management	#19	Plans for data entry, coding, security, and storage, including any
50			related processes to promote data quality (eg, double data entry;
51			range checks for data values). Reference to where details of data
52			management procedures can be found, if not in the protocol
53			
54			
55	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
58			
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1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	N.A.
2	analyses		analyses)	
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	15
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
8				
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10	Methods: Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	15
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
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20				
21				
22	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	15
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	N.A.
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
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32				
33	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	N.A.
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
37				
38	Ethics and			
39	dissemination			
40				
41				
42	Research ethics	#24	Plans for seeking research ethics committee / institutional review	15
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	N.A.
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
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52				
53	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	15
54			participants or authorised surrogates, and how (see Item 32)	
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1	Consent or assent:	#26b	Additional consent provisions for collection and use of	N.A.
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
5				
6	Confidentiality	#27	How personal information about potential and enrolled	14
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	#28	Financial and other competing interests for principal investigators	17, 18
12			for the overall trial and each study site	
13				
14				
15	Data access	#29	Statement of who will have access to the final trial dataset, and	17
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	N.A.
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results	14
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
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33	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	18
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	N.A.
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	Appendices			
42				
43	Informed consent	#32	Model consent form and other related documentation given to	N.A.
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N.A.
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
50				
51				

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