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# Multicentre prospective observational study protocol for radiation exposure from gastrointestinal fluoroscopic procedures (REX-GI study)

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## ABSTRACT

**Introduction** Recently, the use of various endoscopic procedures under X-ray fluoroscopic guidance, such as endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS), enteral endoscopy and stenting, has been rapidly increasing because of the minimally invasive nature of these procedures compared with that of surgical intervention. With the spread of CT and fluoroscopic interventions, including endoscopic procedures under X-ray guidance, high levels of radiation exposure (RE) from medical imaging have led to major concerns throughout society. However, information about RE related to these image-guided procedures in gastrointestinal endoscopy is scarce, and the RE reference levels have not been established. The aim of this study is to prospectively collect the actual RE dose and to help establish diagnostic reference levels (DRLs) in the field of gastroenterology in Japan.

**Methods and analysis** This is a multicentre, prospective observational study that is being conducted to collect the actual RE from treatments and diagnostic procedures, including ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement. We will measure the total fluoroscopy time (min), the total dose–area product ($Gycm^2$) and air-kerma (mGy) of those procedures. Because we are collecting the actual RE data and identifying the influential factors through a prospective, nationwide design, this study will provide guidance regarding the DRLs of ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement.

**Ethics and dissemination** Approval was obtained from the Institutional Review Board of Toyonaka Municipal Hospital (25 April 2019). The need for informed consent will be waived via the *opt-out* method of each hospital website.

**Trial registration number** The UMIN Clinical Trials Registry, UMIN000036525.

## Strengths and limitations of this study

- The large, multicentre, nationwide dataset of radiation exposure doses for gastrointestinal fluoroscopic procedures in gastrointestinal endoscopy gathered in this study will serve as a basis for the development of diagnostic reference levels (DRLs) in Japan.
- Gastrointestinal fluoroscopic procedures have been rapidly increasing in number and complexity, but there are still not enough available local and national DRLs in gastrointestinal endoscopy units.
- These data may not be valid for old models of fluoroscopic systems because this study will include data from fluoroscopic systems with available radiation data.

## INTRODUCTION

Medical radiation is widely used in both medical imaging and radiation treatment. In medical imaging, fluoroscopy employs radiation to show a continuous X-ray image on a monitor and plays a major role in the daily practices of gastroenterology, digestive endoscopy, and hepatobiliary and pancreatic studies. Radiological medical imaging has both benefits and drawbacks for patients. The latter is split into two types: deterministic risks,[1] determined by the threshold dose, as represented by skin injury and stochastic risks, determined by a linear no-threshold model, such as the cancer risk.[2] There have been some reports on radiation-induced skin injury in cardiology and interventional radiology (IVR),[3] but reports from gastrointestinal endoscopy units are rare. However, all medical staff in gastrointestinal endoscopy units need to have correct knowledge of the

appropriate use of medical radiation. Historically, the use of medical radiation has rapidly increased since the 1990s with the spread of CT, and the radiation-associated cancer risk was recognised in the same period, even when the doses of radiation were small.[4–6] In particular, the use of CT has increased approximately 12-fold in the UK and more than 20-fold in the USA in the last 25 years.[7]

The International Atomic Energy Agency, the International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Atomic Radiation and other radiological societies have been attempting to manage medical radiation exposure (RE) according to the 'as low as reasonably achievable' principle by establishing diagnostic reference levels (DRLs) to optimise protection from medical radiation. The concept of DRLs was first introduced by the ICRP 73[8] in 1996. Then, the ICRP emphasised the important role of DRLs as a tool for optimising patient protection.[9 10] Accordingly, the ICRP sets specific target levels for various X-ray-related procedures in 2007.[9] This movement of setting DRLs has been led by radiation-related societies in each region, although the movement has mainly been driven by Western countries. The ICRP 135 recommends that all individuals who are involved in patient procedures with the risk of medical exposure should be familiar with the DRL process as a tool for optimising protection.[11] DRLs are now widely accepted in not only Western countries but also in Japan (Japan DRLs 2015),[12] and DRLs have become the global standard for all procedures that use ionising radiation. Legislation has made it mandatory to establish and record DRLs in Europe, but that is not the case worldwide. The introduction of DRLs in the UK achieved a reduction of approximately 50% in the radiation dose in typical X-ray examinations over 15 years.[13] However, there is still not enough available data on RE for gastrointestinal fluoroscopic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS), small bowel endoscopy and enteral stent placement; these techniques are still being developed and have recently been used with increasing frequency.[14 15]

Our gastroenterologists and endoscopists are still unfamiliar with the DRL concept. Among the guidelines developed by gastrointestinal endoscopy associations, the 2012 European Society of Gastrointestinal Endoscopy guidelines for radiation protection state that the entrance skin dose (approximately equivalent to air-kerma (AK) in this study) and kerma–area product (KAP; approximately equivalent to the dose–area product (DAP) in this study) during diagnostic and therapeutic ERCP are 55–347 mGy and 3–115/8–333 $Gycm^2$, respectively, although information regarding the DRLs of ERCP is limited because this statement is based on only approximately 600 cases of ERCP in 7 reports.[14] No guidelines on RE from the American Society for Gastrointestinal Endoscopy (ASGE) exist, but the ASGE recommends measuring and documenting fluoroscopy time (FT) and radiation dose in all ERCP procedures as a quality indicator (level of evidence: 2C).[16] Although no guidelines for exposure have been developed by the Japan Gastroenterological Endoscopy Society, a description of FT exists in the item regarding ERCP in the Japan Endoscopy Database,[17] which is scheduled to be implemented as a nationwide endoscopic survey in 2020.

Recently, various endoscopic procedures performed under fluoroscopic guidance are rapidly increasing in popularity in gastrointestinal endoscopy units, where the aim is not only diagnosis but also therapeutic intervention. The ICRP recommends that DRLs should be used to manage patient doses during both diagnostic and interventional procedures. There is difficulty in applying the DRL concept to interventional procedures because the RE level depends on the complexity of the procedure and the individual clinical circumstances.[10 18 19] There have been attempts to establish DRLs for IVR procedures, where grouping by disease site may help minimise the wide distribution of RE.[20 21]

The Japanese DRLs were established on a basis of a survey and released in 2015; these guidelines defined the DRL value for fluoroscopically guided interventional procedures as a fluoroscopic radiation dose rate (RDR; interventional reference point dose rate) of 20 mGy/min.[12] However, it did not include information for specific procedures in the field of gastroenterology.[12] Therefore, we aim to prospectively collect actual RE data and identify the influential factors, such as disease site, in the REX-GI (radiation exposure from gastrointestinal fluoroscopic procedures) study and to establish DRLs for the following interventional procedures in gastrointestinal endoscopy units: ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement.

## METHODS AND ANALYSIS

### Aims

The primary aim of this nationwide, prospective study is to collect actual data on RE and identify the factors affecting RE during treatments and diagnostic procedures under different types of fluoroscopic guidance for gastroenterology procedures, including the gastrointestinal, hepatobiliary and pancreatic fields, to serve as a basis for the establishment of DRLs in Japan.

### Design

This is a multicentre, prospective observational cohort study of consecutive patients undergoing the following five treatments and diagnostic procedures under fluoroscopic guidance in the field of gastroenterology: (1) ERCP, (2) interventional EUS, (3) balloon-assisted enteroscopy, (4) enteral metallic stent placement and (5) enteral tube placement. We will examine the procedure time (min), total FT (min), AK (mGy), DAP ($Gycm^2$),[2] total number of roentgenography procedures and RDR (mGy/min) during the procedures. The participating clinicians will manage patients according to the usual clinical practice,

Table 1 Fluoroscopic system and units performing procedures under fluoroscopic guidance

| | | Fluoroscopy device | | | | Fluoroscopy unit |
|---|---|---|---|---|---|---|
| | Number of hospital beds | 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<br>Hitachi<br>Canon Toshiba | Curevista<br>Exavista<br>Ultimax-I | Over-tube<br>Over-tube<br>Under-tube | 2009<br>2013<br>2016 | Radiology |
| Fukui Prefectural Hospital | 872 | Hitachi | Versiflex | Over-tube | 2008 | Endoscopy |
| Kansai Rosai Hospital | 642 | Canon Toshiba<br>Canon Toshiba | Zexira<br>Ultimax-I | Over-tube<br>Under-tube | 2011<br>2017 | Radiology |
| Osaka City University | 891 | Hitachi<br>Hitachi | Curevista<br>Versiflex Vista | Over-tube<br>Under-tube | 2011<br>2015 | Endoscopy<br>Endoscopy |
| Ishikawa Prefectural Central Hospital | 639 | Canon Toshiba | Drex-zx80 | Over-tube | 2016 | Endoscopy |
| Tonan Hospital | 283 | Hitachi<br>Canon Toshiba | Curevista<br>ZEXIRA | Over-tube<br>Over-tube | 2013<br>2016 | Radiology |
| 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<br>Hitachi | Curevista, Versiflex | Over-tube | 2018 | Endoscopy |
| Fukushima Medical University School of Medicine | 778 | Canon Toshiba<br>Canon Toshiba | Zexira<br>FPD1717 | Over-tube | 2012 | Radiology |
| Hyogo Cancer Center | 400 | Hitachi | Curevista | Over-tube | 2019 | Endoscopy |
| Kitano Hospital | 699 | Hitachi<br>Hitachi | Versiflex<br>Curevista | Under-tube<br>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 |

and the patients will undergo the above five procedures. For the analysis, all data, including the related variables and outcome data (tables 1 and 2), will be collected for all patients. The REX-GI study was registered with the UMIN Clinical Trials Registry at http://www.umin.ac.jp/ctr/ under the number UMIN000036525 (registered 1 May 2019).

## Setting

This study will be conducted at seven university hospitals, four cancer centres, nine general hospitals and two municipal hospitals in Japan. The participating hospitals are Toyonaka Municipal Hospital, Kindai University, the University of Tokyo, Fukui Prefectural Hospital, Kansai Rosai Hospital, Osaka City University, Ishikawa Prefectural Central Hospital, Tonan Hospital, Japanese Foundation for Cancer Research, Suita Municipal Hospital, Osaka Rosai Hospital, Osaka General Medical Center, Fukushima Medical University School of Medicine, Hyogo Cancer Center, Kitano Hospital, Tane General Hospital, Japanese Red Cross Medical Center, Kure Medical Center and Chugoku Cancer Center, Nagoya City University Hospital, Toho University Ohashi Medical Center, Osaka International Cancer Institute and Gifu University Hospital (figure 1). Table 1 lists the fluoroscopic systems and units performing procedures under fluoroscopic guidance in each institution. The central sites of

Table 2 Primary outcomes

| Factors | Variables |
|---|---|
| Patients* | ► Procedure type<br>► Age<br>► Sex |
| Fluoroscopic system | ► Fluoroscopic device (company, device model and manufacturing year)<br>► Basic use setting: frame per second and radiation field ($cm^2$) † |
| Radiation exposure | ► Total fluoroscopy time (min)<br>► Air-Kerma (mGy)<br>► Dose–area product ($Gycm^2$)<br>► Total number of roentgenography procedures<br>► Radiation dose rate (mGy/min) |

*We will not collect patient weight or height because we 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.

this study are located at the Toyonaka Municipal Hospital and Kindai University. The participating physicians are gastroenterologists or endoscopists, including all experts and trainees working at all involved hospitals. The quality of the fluoroscopic devices will be regularly monitored according to the procedures in each institution.

## Study population

We will include all patients receiving usual clinical care who undergo the following treatments and diagnostic procedures under fluoroscopic guidance: (1) ERCP; (2) interventional EUS; (3) balloon-assisted enteroscopy; (4) enteral metallic stent placement and (5) enteral tube placement. There is no age restriction. We will exclude patients who do not want to participate in this study via the *opt-out* method on each hospital website and patients who the attending physicians judge to be unsuitable for inclusion in this study.

## Primary outcomes

The primary outcomes will be the total FT (min), RDR (mGy/min), dose–area parameters (AK (mGy) and DAP ($Gycm^2$)) and the total number of imaging studies that the patients who meet the individual inclusion and exclusion criteria will undergo (table 2).

## Secondary outcome

The secondary outcome will be the RE-related factors that affect the radiation dose in each procedure. The details are given in table 3.

## Setting the sample size

According to the preliminary questionnaire survey (data not shown), the numbers of examinations per year in the 8 centres that plan to participate in March 2019 are as follows: 4000 ERCP procedures, 125 EUS procedures, 320 small intestine endoscopy procedures, 44 esophageal stent placements, 150 gastroduodenal stent placements, 75 colorectal stent placements, 180 transanal ileus tube placements and 75 ileus tube placements. The ICRP 135 recommends using data from 20 to 30 facilities to set national DRLs, and a survey for a particular examination in a facility should usually involve the collection of data from at least 20 patients.[11]

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

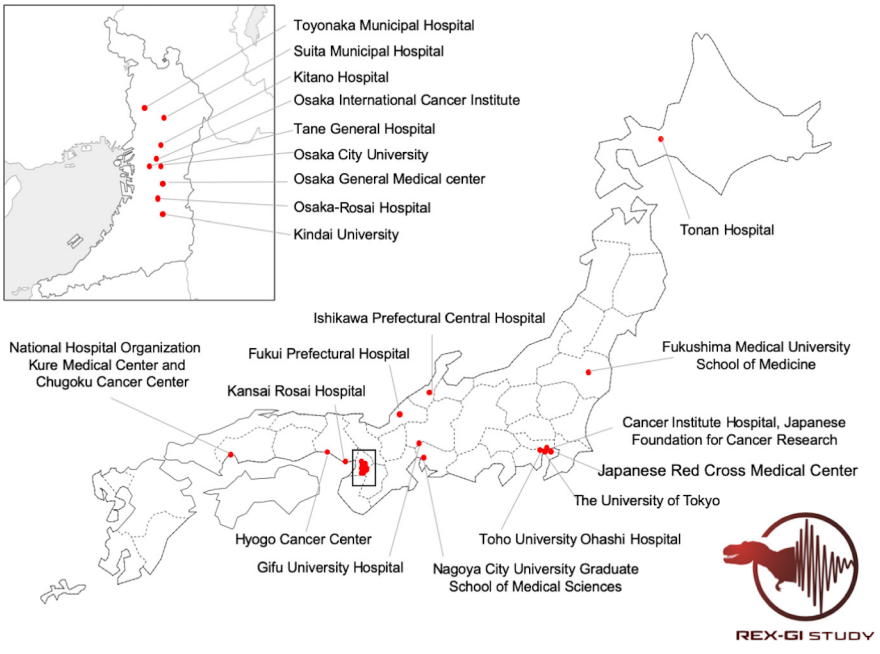


Figure 1 The participating hospitals in this study.

**Table 3** Secondary outcomes

| Procedures | Radiation exposure-related factors |
|---|---|
| ERCP | 1. Surgically altered gastrointestinal anatomy.<br>Billroth I reconstruction, Billroth II reconstruction, Roux-en-Y reconstruction and pancreaticoduodenectomy<br>2. Type of endoscope.<br>3. Naïve papilla.<br>4. Indications for ERCP (including suspicion) are classified into the following five categories:<br>a. 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).<br>b. Distant malignant bile duct stricture (papillary tumour, distal cholangiocarcinoma, pancreatic cancer, etc).<br>c. Proximal malignant bile duct stricture (Hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, gallbladder cancer, etc).<br>d. Pancreatic duct examination (pancreas cancer, intraductal papillary mucinous neoplasm, etc).<br>e. Other diseases apart from those listed above (benign bile duct stricture, pancreatobiliary junction abnormality, etc).<br>5. Total procedure time (min).*<br>a. Cannulation time.<br>b. Treatment time.<br>6. Experience of the HVE or LVE.†<br>7. Facility scale: the number of ERCP procedures per year.<br>8. Whether the fluoroscopic operator is inside or outside in the fluoroscopy room.<br>9. 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 and cholangioscopy).<br>10. Sedation: medication and the depth of the anaesthesia.‡ |
| Interventional EUS | 1. Indication for interventional EUS (EUS-guided hepaticogastrostomy), choledochoduodenostomy, cyst drainage, antegrade treatment, rendezvous technique and pancreatic duct drainage.<br>2. Total procedure time.‡<br>a. Endoscope insertion time.<br>b. Treatment time.<br>3. Facility scale: the number of EUS interventions per year and the number of EUS-guided fine-needle aspiration procedures per year.<br>4. Double stenting (presence or absence of duodenal stenosis).<br>5. Device.<br>6. Scope position.<br>7. Sedation: medication and the depth of anaesthesia. |
| Balloon-assisted enteroscopy | 1. Disease indicating balloon-assisted enteroscopy.<br>a. Hemostatic or bleeding confirmation.<br>b. Crohn's disease.<br>c. Small intestine tumour examination.<br>d. Others.<br>2. Insertion site: perioral or transanal.<br>3. Insertion length (cm).<br>4. Total procedure time (min). |
| Enteral metallic stent placement | 1. Stent location.<br>a. Oesophagus (upper/mid-low/trans).<br>b. Gastro-duodenum (above pylorus/trans pylorus/below pylorus).<br>c. Colon stent (right/left/rectum).<br>2. Total procedure time (min).§<br>a. Endoscope insertion time.<br>b. Treatment time. |
| Enteral ileus tube placement | 1. Disease indicating ileus tube.<br>2. Intranasal ileus tube insertion for ileal obstruction or transanal ileus tube insertion for malignant colonic obstruction.<br>a. Tube insertion length for peroral ileus tube placement (cm).<br>b. The occlusion site for the transanal tube (right/left/rectum).<br>3. Total procedure time (min).¶ |

Continued

Table 3 Continued

| Procedures | Radiation exposure-related factors |
|---|---|

*Cannulation time is defined as the time from endoscope insertion until successful biliary cannulation, and treatment time is defined as the time from successful biliary cannulation until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is removed from the patient (cannulation time+treatment time).
†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.
‡Depth of anaesthesia is divided into three levels based on the RASS, Ramsay Scale and 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 force considered dangerous, RASS score: +2–+4, and SAS score: 6–7 regardless of Ramsay score.
§Endoscope insertion time is defined as the time from endoscope insertion until the initial EUS-guided needle puncture, and treatment time is defined as the time from initial EUS-guided needle puncture until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is 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 is defined as the time from initial guidewire exploration until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time + treatment time).
ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HVE, high-volume endoscopist; LVE, low-volume endoscopist; RASS, Richmond Agitation-Sedation Scale; SAS, Sedation-Agitation Scale.

### Data analysis plan

After obtaining the data, we will perform normality tests. Continuous variables will be expressed as medians with interquartile ranges or means with SD. The categorical variables will be expressed as numbers in each category or as frequencies. To explore surrogate markers of RDR, simple linear regression analysis will be performed to identify the relationships between procedure time, FT and RDR. A multiple linear regression analysis will be performed to identify the factors related to RDR. A p value of 0.05 will be considered statistically significant. All statistical analyses will be performed with JMP software (SAS Institute, Cary, North Carolina, USA).

### Patient and public involvement

Clinical factors related to ERCP and interventional EUS have been retrospectively collected at two sites (Toyonaka Municipal Hospital and Kindai University).[20 22–24] We used those published data to develop plans for the design or implementation of this study and to determine the research question or the outcome measures. No patients were asked to advise us on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants, but we will consider disseminating the results of the research to the relevant patient community.

### Data collection

The clinical factors have been modified to comply with local patient flow and administrative requirements and have been assessed and approved by this study steering committee. We are collecting the password-protected case report forms by email from each institution; these will be de-identified after all data have been collected, and all data queries have been addressed. A unique study identification number will identify each participant and the associated clinical data. Data collection will be performed at 3-month intervals to prevent data loss. Data analysis will take place at the central study site (Kindai University). This study does not require data monitoring due to its nature as an observational study without interventions. Data will be retained for either a minimum of 5 years after the end of this study or for 10 years after publication, whichever is later.

### Patient recruitment and schedule

Patient recruitment will be carried out at the participating hospitals from May 2019 to December 2020.

In 2021, the data analysis, writing and submission of the main manuscript for publication will be carried out.

### Ethics and dissemination

The results of this study will be presented at gastroenterology-, endoscopy- or radiology-related congresses and will be published in a peer-reviewed journal.

## DISCUSSION

Currently, the establishment of DRLs is an international requirement for protection from medical radiation. For diagnostic radiology, national and regional DRLs are usually set at the 75% percentile of the distribution of a typical sample dose.[25] All physicians or medical staff who are involved in radiological imaging or procedures under fluoroscopic guidance should be familiar with the DRL process as a tool for optimising protection. In addition, separate DRLs must be established for each country and/or region because the equipment and procedure protocols can vary among different regions.[25] However, the amount of RE depends on the procedure complexity, patient anatomy, lesion characteristics, disease severity[11] and type of fluoroscopic devices[20]; thus, setting the upper limit of radiation use by applying uniform standards is difficult. Generally, DRLs are not dose limits and do not help distinguish between good and poor medical practices.[25] Therefore, a high demand exists for a large

amount of real-world evidence. The 2015 Japan DRLs state that the methods for establishing DRLs not only include setting radiation dose levels but also includes determining the dose quantities and units used to set the DRLs, thus standardising the methodology for dose measurements, data collection and identification of the applications of DRLs.[12]

Unfortunately, most gastroenterologists are unfamiliar with not only DRLs but also radiation protection because information on RE from gastrointestinal medical treatment is currently very scarce, and few RE standards, including DRLs, have been established worldwide. Given this background, the REX-GI study is planned as an observational, nationwide study in Japan. Our results will help to promote radiation optimisation and patient radiation protection in gastroenterology studies, such as digestive endoscopy, and hepatobiliary and pancreatic procedures.

## Publication

After completion of this study, a main manuscript will be prepared to present the results and will be submitted to a clinical journal for peer review. This study will ensure that the public has access to the published data.

## Consent for publication

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


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**Contributors** TN, SH (Toyonaka Municipal Hospital) and MT (Kindai University) designed this study. MH (Kindai University) critically reviewed the protocol. TN, SH (Toyonaka Municipal Hospital), MT (Kindai University), HK (the University of Tokyo), KH (Fukui Prefectural Hospital), SY (Kansai Rosai Hospital), HM (Osaka City University), HD (Ishikawa Prefectural Central Hospita), HI (Tonan Hospital), TYoshio (Cancer Institute Hospital), KN (Suita Municipal Hospital), TYamada (Osaka Rosai Hospital), TYakushijin (Osaka General Medical Center), TT (Fukushima Medical University School of Medicine), HT (Hyogo Cancer Center), AK (Kitano Hospital), SA (Tane General Hospital), YI (Japanese Red Cross Medical Center), TK (National Hospital Organization, Kure Medical Center and Chugoku Cancer Center), YH (Nagoya City University Graduate School of Medical Sciences), IM (Toho University Ohashi Medical Center), KI (Osaka International Cancer Institute), TI (Gifu University Hospital), KM and MI (Toyonaka Municipal Hospital) participated in this study and recruited the patients.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This observational study will be conducted in accordance with the principles of the Declaration of Helsinki, and approval has been obtained from the Institutional Review Board of Toyonaka Municipal Hospital (25 April 2019) and the institutional review board of each participating facility. The need for informed consent will be waived via the *opt-out* method on each hospital website.

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