First-in-Human (FIH) trials: Role of the CRC

Shinobu Araki
National Cancer Center Hospital
Clinical Research Coordinator
CRC, Department of Experimental Therapeutics (DET)

Presentation overview

- Creating a foundation for conducting FIH trials
- Launching of the FIH trial and materializing the trial
- Conducting the FIH trial

Creating a foundation for conducting FIH trials

【Why is it important to build a foundation for FIH trials?】

① To make the FIH trial safe and secure for patients

It is necessary to establish a system that can respond to unexpected events.

② To ensure accurate data collection

It is necessary to understand the importance of each type of data
and create a system for reliably collecting data.

③ To match the speed of FIH trials

A system that can be used to start trials in time for the full site opening is required.

【CRC】

★ System used in our hospital

Clinical Research Coordinator Department: 41 CRCs + 9 assistants

Divided into 4 teams according to disease

→ Development of Experimental Therapeutics (DET) team (in charge of Phase 1 trial): CRC 9 individuals

Results for FY 2021	CRC Dept. Overall	DET
Number of tested cases	811	252
Number of new trials		30 (15 FIH)

Number of trials overseen by each DET CRC: 10 on average

Number of patients overseen by each DET CRC: 15 on average

Only one CRC is in charge from the start of the trial, through patient work, and to the end of the trial

【Trial sites】

Hospitalized **Phase 1 (FIH) trial specialized ward (32 beds)**	**Outpatient facility** **Outpatient department of DET (1 booth) + outpatient department of each clinical department** **Outpatient treatment center (68 beds)**
First dose: while hospitalized	After the end of the DLT period: generally outpatient management
≪Role of the ward≫ Initial administration and adverse event management at the time of administration Frequent PK blood sampling and data collection such as ECG Subject guidance and psychological follow-up at the time of initial introduction to the trial	≪Role of outpatient facility≫ Management of late-onset adverse events Outpatient regular administration Continuous subject guidance and psychological follow-up
≪What CRCs do≫ ・Study session on basic knowledge of clinical trials (summary of clinical trials, management of adverse events, data collection, etc.) ・Information session for new trial (dose method of investigational product (IP), characteristic adverse events, etc.)	≪What CRCs do≫ Information session for new trial (dose method of IP, characteristic adverse events, etc.)

【Related departments】

Clinical laboratory, pharmacy, pathology, ophthalmology, cardiology, dermatology...

"Can your department inspect this?"
"Can you dispense this medicine?"
"Can you use this material (injection needle/IV route)?"
"Can the patient visit this department when an adverse event occurs?"
→ Often requires special inspections and procedures

Know if you can handle these questions to some extent
Set up a "contact point for asking questions" in each department
In some cases, adjust for alternatives and propose them to the client

【Clinical trial office】

ICF: Informed Consent Form
SAE: Serious Adverse Event

Confirmation of IRB submission documents

such as informed consent form (ICF), serious adverse events (SAE), serious deviations, and continuous examination.

→These will likely occur in FIH trials

SAEs due to unknown symptoms, deviation due to complicated procedures,
ICF revisions due to frequent Protocol and Investigators Brochure revisions.

What should I report, and when should I report it?

The clinical trial office is a strong ally
and provides help with documentation and paperwork.

【Emergency systems】

FIH trials are inherently unpredictable

Emergency systems (Ex: cooperation with ICU) is important for addressing sudden changes due to high-risk study drugs.

Example: CAR-T therapy with high risk of cytokine release syndrome (CRS)

CRS: Cytokine Release Syndrome

Hospital	• ICU staff understands the dosing schedule
Dosage	• ICU staff monitors the subject status periodically
Sudden change	• Patient is sent to ICU, and treatment is started

【Night/holiday emergency system】

When the subject becomes ill at night or during a holiday

Initial response: Doctor on duty

The patient's basic information are described in the medical records.

Example) ○○ trial (△△△ antibody)　Cycle 2 day 15

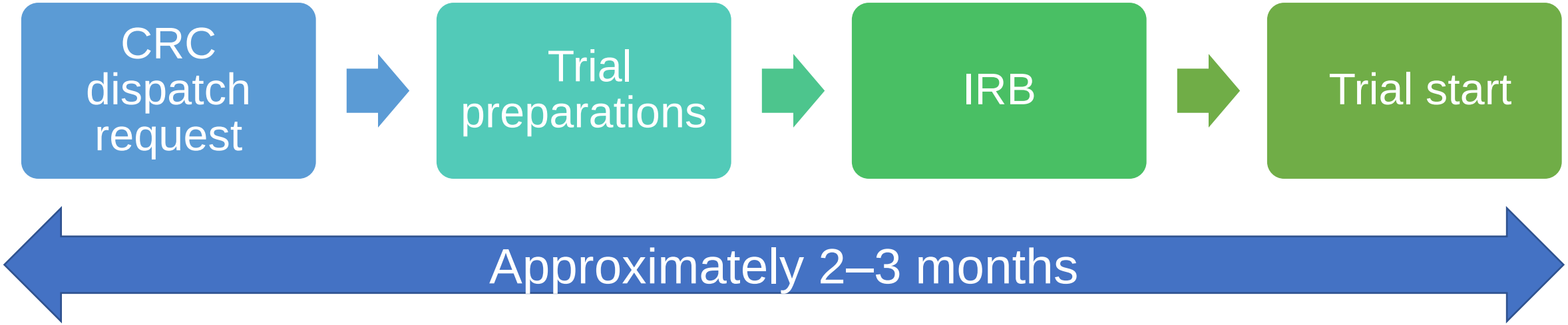
prohibited medication: □□□

After handing over to the relevant department: PI or SI

If the CRC also cannot respond,

- Protocol and SAE reporting procedures are stored in the cloud
- Creating a simple procedure for reporting SAE

【Creating a foundation for conducting FIH trials】



- To launch a truly feasible FIH trial in a short period of time,

→a solid foundation is necessary

Launch of the FIH trial

Materialization of the trial

【Features of FIH trials】

Even if the protocol is completed, the contents are vague.

Procedures that are not specifically fixed…
Feasible or suspicious procedure…
Procedures that place a heavy burden on the subject…

【Top three troublesome protocols】

1st place: Pharmacokinetics (PK) allowance of ± 30 s

2nd place: Combination therapy with two drugs, replace the needle for each drugs
(for complete replacement from the needle to route)

3rd place: No water intake for 1 h before and after oral administration

CRC viewpoint (real-world perspective)

Evaluate safety and feasibility, and creating a feasible trial is a skill for CRCs

【Bringing complex protocols to actionable procedures：staff】

Implementation order ① ECG → ② VS → ③ PK					
Day	**Schedule time**		**PK**	**ECG,**	**Urinary storage**
C1D1	pre	8：30—9：00	：	□ Three times consecutively	Urine storage ①9：00–15：00 urine volume（ mL） ②15：00-21：00 urine volume（ mL）
	Administration 09:00				
	30 min (±10 min)	9:30	：	□ Three times consecutively	
	1 h (±10 min)	10:00	：	□ Three times consecutively	
	2 h (±10 min)	11:00	：	□ Three times consecutively	
	4 h (±10 min)	13:00	：		
	24 h (±60 min)	21:00	：	□ Only once	

Protocol

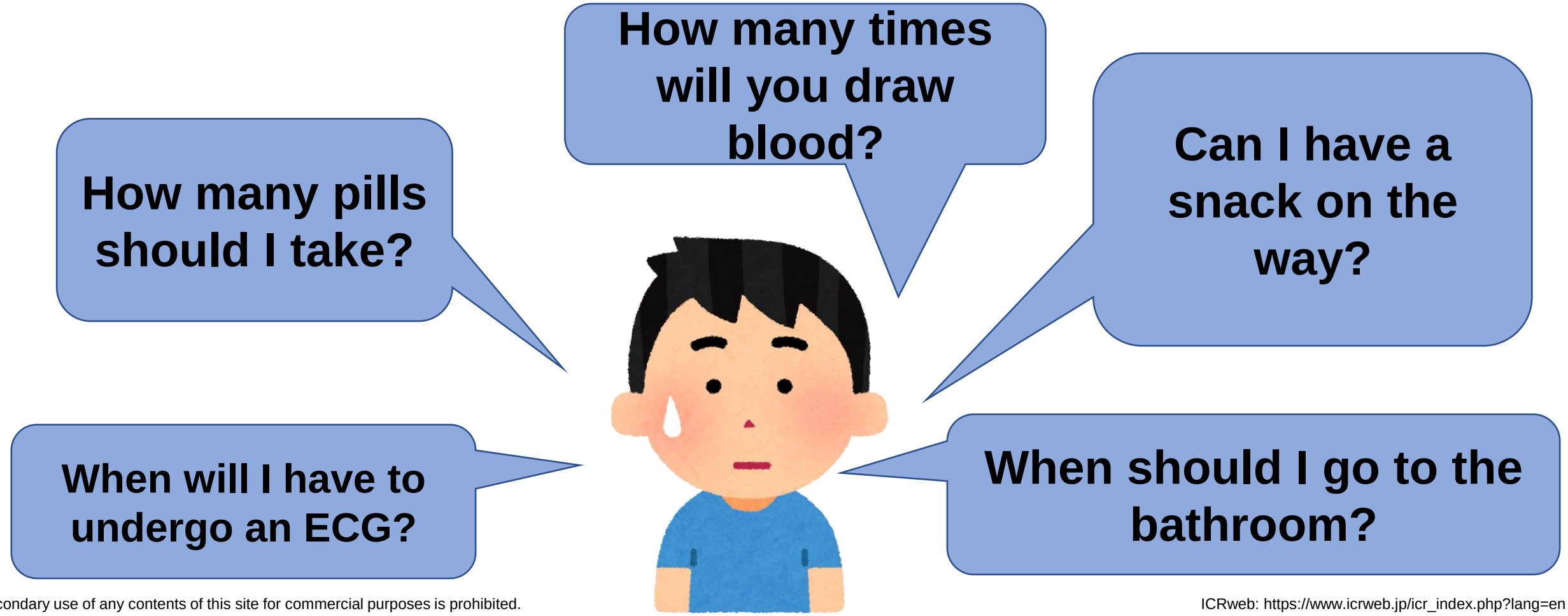
Contents of all pages

Aggregate into one table

- PK time points
- ECG time points
- VS, ECG, PK order
- Other inspections

【Bringing complex protocols to actionable procedures: subjects】

Subjects on the first administration day



IP ABC, cycle 1: 1st day

)

Oral dosage specifics	IP ABC 30 mg: Taken once per day 1 cycle is 28 days: 3 days oral intake, 4 days off
Notes	**Fasting for 2 h before taking the medicine and 1 h after taking the medicine. Only consumption of water is permitted.**

Wake up

- Weight
- Temp
- Blood and urine samples

8:30-First dose

- ECG
- Blood sample

Take a needle for blood collection

10:30

Oral dose of IP ABC

11:00 (± 10 min) Oral dose after 30 min blood sample

11:30 (± 10 min) Oral dose after 30 min

ECG blood sample

12:30 (±15 min) Oral dose after 2 h

ECG Blood sample

Summarize the subject's daily schedule in one table

Timing of medication

PK time points

ECG time points

etc.

Daily flow

Daily flow

Conducting the FIH trial

【Incorporating candidate cases】

★ Weekly conference

- Select a trial that can be registered
- List of referral patients from each clinical department and other facilities
- Sharing of trial progress
- Selection of candidate trials based on patient information

★ CRC grasps the following and announces:

- Detailed inclusion and exclusion criteria
- Current entry availability (remaining cohort slots)

【Confirmation of eligibility】

Doctor's point of view (medical) and CRC's point of view (character)

Doctor’s point of view (medical)
Disease (type of cancer, genetic mutations, etc.)
General status (test values, complications, etc.)
Treatment history, etc.

CRC’s viewpoint (character)
Understanding of clinical trials
Compliance
Social background (work and family, area), etc.

【Schedule management】

Schedules for FIH trials	
Frequently open/close cohort	Confirm with the client whether subject should be included
Long hospitalization at the first dose	Confirm whether the bed is available
Frequent need to visit the hospital	Must confirm during holidays (especially extended ones)
Several special tests	Must make necessary reservations

Ex. schedule management	
IP dosage interval	2 weeks (±3 days)
Doctor's examination days	Mon/Wed
Patient convenience	Wishes for Mon
Days C1D1 can be started	Mon–Wed only

Important for reducing the burden on the subject, collecting accurate data, and progressing the trial !!

【Data management: timely data entry or urgent EDC entry】

FIH trial data entry deadline example

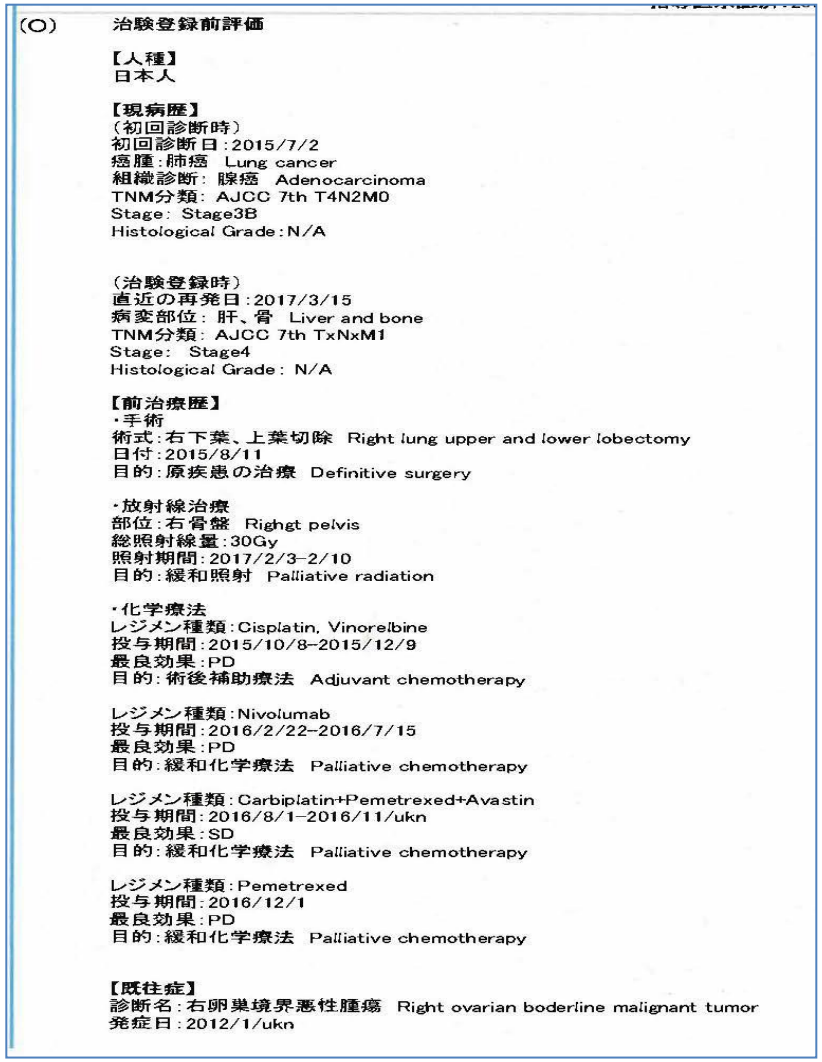
- Before regular global meetings (every 2 weeks)
- Before the dose escalation meeting for the next cohort opening (every 2–3 months)
- Before data cleaning of the entire trial (irregular)

Characteristics of subjects participating in the FIH trial

- Long treatment history
- Complex medical history
- Many concomitant therapies
- Many AEs
- Many SAEs・・・

EDC: Electronic Data Capture

【Data management: efficient data entry】



(O) 治験登録前評価

【人種】
日本人

【現病歴】
（初回診断時）
初回診断日：2015/7/2
癌腫：肺癌 Lung cancer
組織診断：腺癌 Adenocarcinoma
TNM分類：AJCC 7th T4N2M0
Stage：Stage3B
Histological Grade：N/A

（治験登録時）
直近の再発日：2017/3/15
病変部位：肝、骨 Liver and bone
TNM分類：AJCC 7th TxNxM1
Stage：Stage4
Histological Grade：N/A

【前治療歴】
・手術
術式：右下葉、上葉切除 Right lung upper and lower lobectomy
日付：2015/8/11
目的：原疾患の治療 Definitive surgery

・放射線治療
部位：右骨盤 Righgt pelvis
総照射線量：30Gy
照射期間：2017/2/3-2/10
目的：緩和照射 Palliative radiation

・化学療法
レジメン種類：Cisplatin, Vinorelbine
投与期間：2015/10/8-2015/12/9
最良効果：PD
目的：術後補助療法 Adjuvant chemotherapy

レジメン種類：Nivolumab
投与期間：2016/2/22-2016/7/15
最良効果：PD
目的：緩和化学療法 Palliative chemotherapy

レジメン種類：Carbiplatin+Pemetrexed+Avastin
投与期間：2016/8/1-2016/11/ukn
最良効果：SD
目的：緩和化学療法 Palliative chemotherapy

レジメン種類：Pemetrexed
投与期間：2016/12/1
最良効果：PD
目的：緩和化学療法 Palliative chemotherapy

【既往症】
診断名：右卵巣境界悪性腫瘍 Right ovarian boderline malignant tumor
発症日：2012/1/ukn

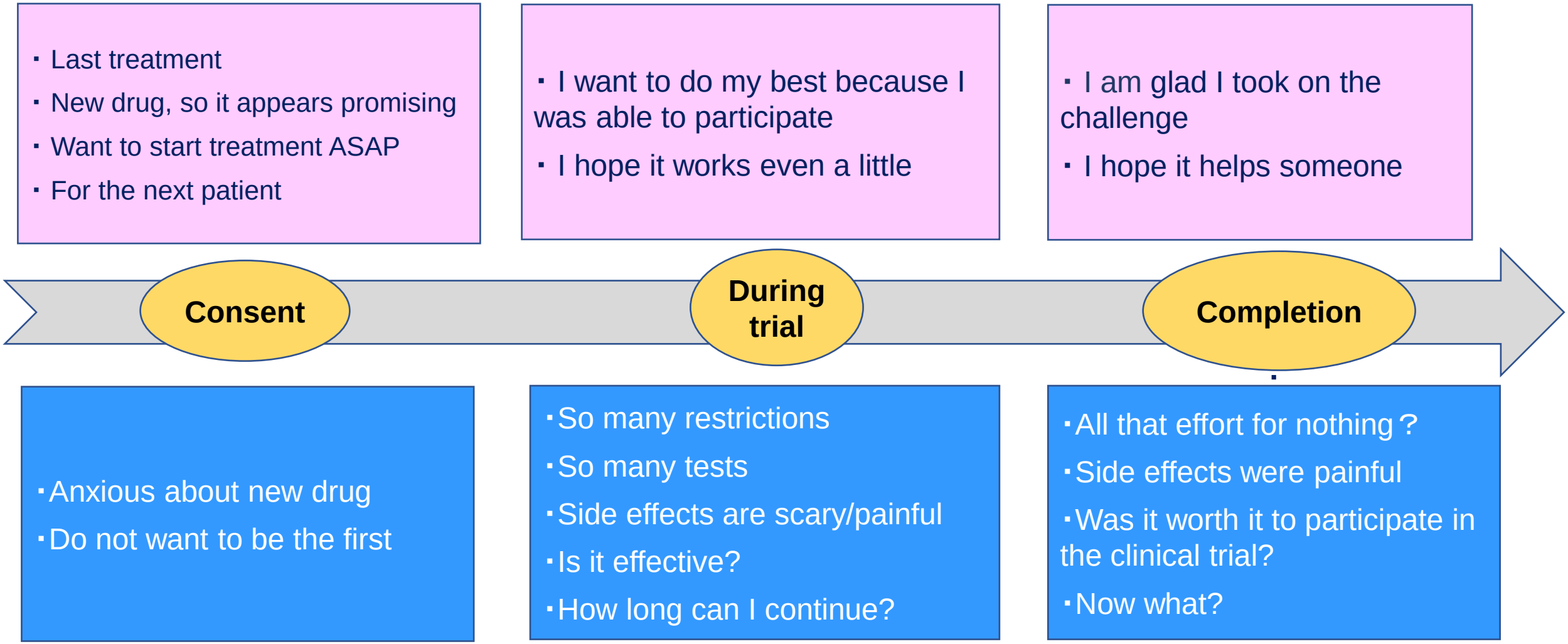
Current medical history, medical history, previous treatment history, combination drugs, etc.

A template should be created for common items that require EDC input in any trial

- Speed up EDC input
- Error reduction when inputting EDC
- Guaranteeing the quality of the original material

【Subject care】

Subject's psychological changes in FIH trial



【Subject care】

- The FIH trial does not greatly differ from other Phase I–III trials.
- Because FIH has a strong research aspect, we value the relationship between people.
- Counsel patients so that they do not regret participating, regardless of whether the trial was effective

Wrap-up

So, what is the role of CRCs in FIH trials?

There are countless things we must do.

For our present patients and
for the patients who will come after them.

After each piece falls into place and the overall effort takes shape,
you will start to understand the value of participating in FIH trials.
Let us try our best together.