Long-term Outcomes of Anti-viral Therapies in Patients with Chronic Viral Hepatitis B : A Multicenter, Real-world Study (OASIS)

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Contents

1 Scientific Background

Chronic hepatitis B (CHB) is an infectious disease caused by hepatitis B virus (HBV), which can last longer than six months, and characterized primarily by liver injury. Epidemiological data estimate that over 70 million people in China are currently infected with HBV, of whom more than 20 million have developed CHB. Since 2012, the annual incidence of CHB in China has exceeded 1.05 million cases [1,2]. In the liver of CHB patients, direct effects of viral replication and transcription activity, together with virus-triggered host antiviral immune responses, lead to persistent inflammatory cell infiltration in the liver, ongoing hepatocellular injury and necrosis, and activation of collagen fiber proliferation and deposition. This results in abnormal liver function, progressive hepatic fibrosis, and eventually cirrhosis or hepatocellular carcinoma (HCC) [3,4]. CHB imposes a heavy disease burden and remains a major public health challenge in China.

After HBV infects the human body, its partially double-stranded relaxed circular DNA (rcDNA) together with HBV DNA polymerase enters into the nucleus. With the assistance of host DNA repair mechanisms, rcDNA is converted into covalently closed circular DNA (cccDNA), which serves as the template for viral replication. cccDNA binds to host histones and non-histone proteins to form a highly stable viral minichromosome [5,6]. Due to the long half-life of cccDNA, progeny rcDNA generated through transcription and reverse transcription can replenish the nuclear cccDNA pool without requiring new viral entry, it maintains a persistent transcriptional template. When cccDNA continues to exist, some progeny rcDNA replenishes the nuclear cccDNA pool, and others acquire an envelope through the endoplasmic reticulum–Golgi complex to form viral particles that are secreted from hepatocytes into the bloodstream [5,7].

Because of this unique and complex replication mechanism, HBV cannot be completely eradicated. The persistence of cccDNA in hepatocyte nuclei means that even patients who achieve apparent recovery, as indicated by serological markers, remain at lifelong risk of viral reactivation [5,8].

Currently, the main antiviral drugs used in CHB include interferons (IFNs) and nucleos(t)ide analogues (NAs) [2,9–11]. NAs mainly inhibit viral replication by blocking the reverse transcription process. They are administered orally, easy to use, and generally well tolerated [5,18,19]. However, because NAs do not directly inhibit cccDNA transcriptional activity, they fail to effectively suppress the production of viral proteins such as HBsAg expression. As a result, HBsAg declines slowly during treatment, and the annual clearance rate of HBsAg remains only 0–

1.3% under the long-term NAs therapy, and this means CHB patients require indefinite treatment [5,12,13]. IFNs exert a dual effect by enhancing host immune responses and directly inhibiting viral replication at multiple stages [14–16]. In addition to suppressing viral replication, IFNs also inhibit cccDNA transcription, promote cccDNA degradation, and facilitate the clearance of HBV-infected cells, thus favoring viral elimination. In some patients, HBsAg declines rapidly during IFN therapy. Previous studies, varying by selected populations, reported HBsAg seroclearance rates of 2.8–7% after 48 weeks of IFN monotherapy, which are higher than those observed with NAs monotherapy. And its benefits may continue even after IFN discontinuation [17–19]. However, IFNs require subcutaneous injection and are associated with adverse effects such as bone marrow suppression and flu-like symptoms, leading to relatively poor tolerability.

Pegylated interferon (PegIFN) in combination with NAs has become a recent focus of clinical practice and research. As these drugs target different aspects of the viral life cycle, their combination may produce additive or synergistic effects, potentially improving efficacy [19,20]. Combination therapy with PegIFN and NAs can be applied either as initial therapy or sequential therapy. In the former, PegIFN and NAs are administered together as first-line treatment in treatment-naïve CHB patients. In the latter, PegIFN is added to or substituted for NAs in patients who have already achieved a virological response with NAs. Whether PegIFN plus NAs provides clear additional benefit compared with PegIFN or NAs alone, or whether it merely increases patient burden with limited additional benefit, remains controversial. Details regarding treatment indications, timing of initiation, and duration of combination therapy remain debated. Regarding this issue, existing studies are often limited by sample size, geographical region, or study population, provide inconsistent results. Most studies include fewer than 1,000 patients, with follow-up typically limited to 1–2 years. Due to limited sample size and duration, evaluation of long-term outcomes such as HCC incidence or decompensated cirrhosis is difficult. Consequently, most studies use HBsAg loss as the primary endpoint.

For example, retrospective analyses of previous studies show that although PegIFN plus NAs as initial combination therapy yields significantly higher HBsAg clearance rates than NA monotherapy, comparisons with PegIFN monotherapy yield inconsistent results. Sequential PegIFN therapy after NAs also improves HBsAg clearance compared with continued NA monotherapy, but few studies compare it directly with PegIFN monotherapy [12,13,17,20–27]. Improvements in fibrosis observed with PegIFN sequential therapy suggest additional benefit over NAs alone, but comparative data remain limited. Patients treated with PegIFN show a lower

incidence of HCC compared with NA monotherapy, but comparative data among PegIFN monotherapy, sequential therapy, and initial combination therapy are lacking. Regarding treatment duration, whether extending PegIFN therapy beyond the currently recommended 48 weeks provides additional benefit remains uncertain. Some studies report that extending therapy to 72 or 96 weeks in HBeAg-negative patients yields higher HBsAg clearance rates than 48 weeks, though without statistical significance due to small sample sizes [28,29]. Other studies indicate that extending sequential PegIFN therapy to 96 weeks after NA-induced HBeAg clearance does not significantly improve HBsAg clearance compared with 48 weeks [24].

Therefore, the advantages and disadvantages of different antiviral strategies for CHB—particularly their effects on long-term outcomes such as HCC and decompensated cirrhosis—remains insufficient. Large-scale, long-term, high-quality clinical studies are urgently needed to provide robust evidence for optimizing antiviral regimens.

This study aims to establish a nationwide, multicenter, real-world cohort to compare long-term outcomes under different treatment regimens. The goal is to generate high-quality evidence to guide treatment and follow-up of chronic viral hepatitis, support optimization of therapeutic strategies, and accelerate progress toward a functional cure.

2 Aims

To explore the long-term outcomes of antiviral therapy for CHB with the incidence of HCC as the primary endpoint, in order to identify optimal clinical decision-making strategies for the management of CHB.

3 Study design

This is an observational, multicenter, real-world study led by Huashan Hospital. Approximately 98 sub-centers are expected to participate. Randomization and blinding are not involved in this study. It will only observe and collect data related to the changes of clinical indicators during routine treatment. The physicians will make clinical decisions based on the applicable guidelines and evidence at the time of enrollment, combined with clinical experience and patient-specific conditions. No additional interventions will be imposed, and clinical decisions will not be influenced by this study.

The study consists of three cohorts (Figure 1):

Prospective cohort (PS cohort): Patients enrolled before the implementation of Protocol Version 3.0 who were planned or currently undergoing antiviral therapy. Clinical data will be prospectively collected for five years after informed consent has been obtained. The total follow-up period will last five years.

Retrospective-prospective cohort (RPS cohort): Patients received antiviral therapy whose initial clinical visit occurred before Protocol Version 3.0 but signed informed consent after its implementation. The study will retrospectively collect treatment and examination records from baseline (defined as the date patient first visited the study center for CHB starting from September 2020, with concurrent HBV DNA, liver function, and abdominal ultrasound results) and will prospectively collect subsequent clinical data up to five years from baseline. The total follow-up period will last five years.

Retrospective cohort (RS cohort): Patients receiving antiviral therapy whose clinical records from September 2020 until the implementation of Protocol Version 3.0 will be retrospectively collected.

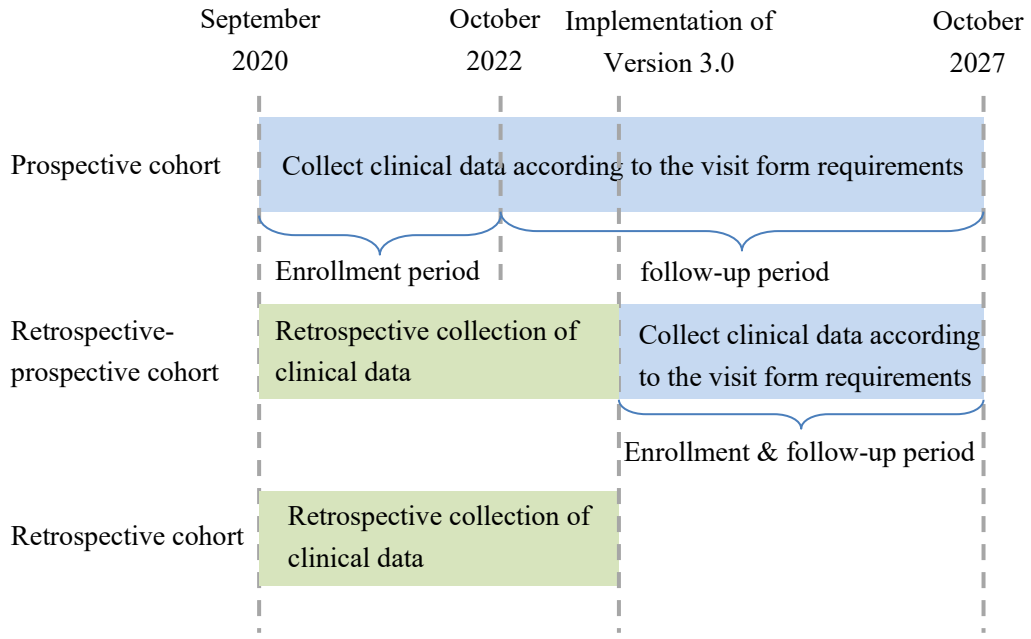

Figure 1 Schematic diagram of the study design

Patients enrolled at sites before Version 3.0 are assigned to the PS cohort, those enrolled before Version 3.0 belong to the RS cohort, and whether to belong to the RPS cohort is depending on

patients' willingness. Patients at newly added sites after Version 3.0 are included in the RS cohort, and may, depending on patients' willingness, be included in the RPS cohort.

4 Eligibility Criteria, Exclusion Criteria, and Withdrawal Criteria

4.1 Inclusion Criteria

1) Chronic HBV infection (HBsAg positive for ≥6 months, or <6 months with liver histology consistent with CHB and other liver diseases excluded);
2) Age ≥18 years;
3) Planned or currently receiving potent low-resistance NAs [entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), or tenofovir amibufenamide (TMF)], or planned to receive PegIFNα-2b, either treated or treatment-naïve;
4) Written informed consent.

4.2 Exclusion Criteria

1) Hepatocellular carcinoma (diagnosed or planned for treatment) or liver failure at baseline;
2) Concurrently participating in other interventional clinical trials;
3) Any other conditions deemed unsuitable by investigators or preventing compliance with study requirements.

4.3 Withdrawal Criteria

1) Request to withdraw at any time;
2) Investigators determine continuation is not in the patient's best interest;
3) Occurrence of clinical Objectives, including HCC, liver transplantation, or death;
4) Lost to follow-up.

4.4 Lost to Follow-up Criteria

Patients in the PS or RPS cohort who fail to return within 13 months and cannot be contacted after at least two phone calls (each at least 24 hours apart) or other attempts via registered mail, courier, or email will be classified as lost to follow-up.

Exception: If patients notify investigators in advance of inability to attend a scheduled visit or examinations due to special reasons, this is not considered lost to follow-up. In such cases,

investigators should encourage patients to undergo examinations at other medical institutions and provide results through appropriate forms.

5 Sample Size Estimation

As an observational real-world study, sufficient sample size is needed to reflect real-world conditions and balance patient heterogeneity. Based on the number of participating centers and patient flow, approximately 33,000 patients are expected to be enrolled for analysis.

6 Study Procedures

6.1 Clinical Information to be Collected

6.1.1 The collection information and time point of PS Cohort

Starting from September 2020, outpatient or inpatient patients with CHB who meet inclusion criteria and have been screened through the exclusion criteria will be enrolled after informed consent. Baseline data and scheduled follow-up assessments will be collected at fixed time points after treatment initiation. Recommendations are based on the guidelines and clinical evidence. Actual schedules may be adjusted by treating physicians. No additional visits will be imposed by the study [2].

A recommended follow-up schedule and assessments are summarized in Table 1.

Table 1 Study visit table

	Baseline	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Study week	0	4±1	12±2	24±4	36±4	48±4	72±4	96±4	120±4	144±4	168±8	192±8	216±8	240±8
Time point	0	1m	3m	6m	9m	1y	1.5y	2y	2.5y	3y	3.5y	4y	4.5y	5y
Demographics	★													
Height & weight	★													
Medical history	★													
Family history	★													
Clinical assessment														
Symptoms and signs	★			★	★	★	★	★	★	★		★		★
Treatment regimen	★			★	★	★	★	★	★	★		★		★
Clinical events[a]	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Laboratory tests														
Quantitative HBsAg	★	★	★	★	★	★	★	★	★	★	★	★	★	★
HBeAg, anti-HBe, anti-HBc, anti-HBs	★	★	★	★	★	★	★	★	★	★	★	★	★	★
HBV DNA	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Complete blood count	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Hepatic panel	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Creatinine	★			★		★		★		★		★		★

AFP & CEA	★			★		★		★		★		★		★
INR & PT	★			★		★		★		★		★		★
TC, TG, HDL-c, LDL-c	★			★		★		★		★		★		★
Glucose	★			★		★		★		★		★		★
HbA1c	**As clinically indicated [c]**													
Creatine kinase														
Electrolytes（K，P，Ca）														
Urinalysis														
Imaging[b] and liver pathology														
Transient elastography	★			★		★		★		★		★		★
Abdominal ultrasound	★			★		★		★		★		★		★
Abdominal MRI	**As clinically indicated [b,c]**													
Abdominal CT	**As clinically indicated [b,c]**													
Liver biopsy	**As indicated for clinical events [a] or by clinical need**													

a Clinical events include decompensated cirrhosis, HCC, death, or liver transplantation

b If abdominal ultrasound is unavailable, MRI or CT may be used as an alternative and will be treated as required completion items

c The study does not mandate MRI/CT/liver histology, but when these tests are performed in routine care, their results will be collected to enrich observational data

6.1.2 The collection information of RPS Cohort

6.1.2.1 Retrospective data collection

Clinical records from baseline up to the date of informed consent will be collected retrospectively, according to the study visit table (Table 1). Any items not performed in routine care will be recorded as missing data.

6.1.2.2 Prospective data collection

Subsequent visits will follow the windows specified in the study visit table (Table 1). The initial prospective visit will depend on the interval between baseline date and the consent date.

Example: If baseline was October 2020 and consent was signed in December 2023 (an interval of 3 years), prospective follow-up would begin at V9 (corresponding to 3 years).

6.1.3 The collection information of RS Cohort

Clinical data generated between September 2020 and the implementation of Protocol Version 3.0 will be retrospectively collected (items based on the study visit table, Table 1, with time points recorded according to when they actually occurred). Any items not collected in routine practice will be recorded as missing data.

6.2 Follow-up Management and Measure to Ensure Patient Compliance

The study aims to achieve a follow-up rate of more than 80%. As this is a non-interventional study, measures will be taken to maximize patient compliance. At both initial and follow-up visits, patients will receive education and reminders to attend subsequent scheduled follow-ups on time. The study database system includes functions that regularly notify site investigators of recommended follow-up time points, prompting physicians to conduct visits and complete data collection and entry as needed. In addition, patient education booklets containing follow-up record forms will be distributed, encouraging patients to adhere to regular follow-up, consistently document their test results, and gain a better understanding of their disease status and treatment outcomes.

7 Study Termination Criteria

The study will be terminated if:

1) Major flaws or serious deviations occur during implementation, making evaluation infeasible.
2) Adverse events or serious adverse events related to treatment occur during the study, and investigators deem it unsafe to continue.
3) Regulatory authorities, government departments, or ethics committees request suspension

or termination of the study.

4) Other circumstances arise that investigators consider make continuation inappropriate or impractical.

8 Efficacy Evaluation

8.1 Effectiveness

8.1.1 Primary Objectives:

To compare the 5-year incidence of HCC under different treatment regimens.

8.1.2 Secondary Objectives:

1) Compare the 1-year, 2-year, 3-year, 4-year, and 5-year rate of HBsAg seroclearance and HBsAg seroconversion under different treatment regimens.
2) Compare the 5-year incidence of decompensated cirrhosis and its complications under different treatment regimens
3) Compare the 5-year incidence of cirrhosis under different treatment regimens
4) Compare proportion of patients with improvement or progression of liver fibrosis under different treatment regimens
5) Compare the 5-year incidence of liver transplantation under different treatment regimens
6) Compare the 1-year, 2-year, 3-year, 4-year, and 5-year HBsAg levels, the decline changes of HBsAg from baseline, the rate of HBeAg seroconversion, the decline changes of HBV DNA from baseline, and the proportion of HBV DNA undetectable (<20 IU/mL) under different treatment regimens
7) Compare the relapse rate after treatment cessation under different treatment regimens

8.1.3 Exploratory Objectives:

Describe the demographic characteristics of patients in the real-world clinical setting.

8.1.4 Methods for Assessing Efficacy Endpoints:

8.1.4.1 HCC: According to the 2019 National Health Commission diagnostic criteria for hepatocellular carcinoma, a diagnosis of HCC will be considered confirmed when either pathological or clinical criteria are met. Pathological confirmation requires diagnosis by two or more pathologists as hepatocellular carcinoma. Clinical diagnosis requires at least one typical imaging features about nodules and liver cancer on dynamic contrast-enhanced MRI, dynamic contrast-enhanced CT, contrast-enhanced ultrasound, or hepatocyte-specific contrast (Gd-EOB-DTPA) MRI; a diagnosis is established if either of the following is satisfied: 1) any nodule size >2 cm with one typical imaging feature; 2) all nodules sizes ≤2 cm with two typical imaging features. During follow-up, any HCC event must include recording of pathology reports (including

subtype, differentiation, and presence/distribution of intravascular tumor clusters) or imaging descriptions (including imaging modality that showed typical HCC features and nodule size), and scanned copies of original reports must be provided for centralized verification by the study team.

8.1.4.2 Decompensated cirrhosis: According to 2019 Chinese Society of Hepatology guidelines on the management of liver cirrhosis, a diagnosis of cirrhosis will be considered confirmed when either pathological or clinical criteria are met, and when clinical manifestations suggest decompensated will be considered to be decompensated cirrhosis [31]. Pathological confirmation requires diagnosis by two or more pathologists as decompensated cirrhosis. Clinical criteria require that endoscopic evidence of esophagogastric varices, ultrasound or CT findings suggesting cirrhosis or portal hypertension, or liver stiffness measurement [LSM] values reaching corresponding thresholds. Clinical features of decompensation include ascites, variceal hemorrhage, spontaneous bacterial peritonitis/sepsis, hepatic encephalopathy, or hepatorenal syndrome, confirmed by laboratory tests, imaging, or clinical scoring systems. On occurrence of decompensated cirrhosis during follow-up, investigators must document pathology (including number of pseudo-lobules, inflammation and fibrosis staging), or supporting ancillary test results (e.g., presence of varices, imaging features suggesting cirrhosis/portal hypertension, specific LSM values, ascites, variceal bleeding), and laboratory or clinical records indicating decompensation (e.g., temperature, cognitive assessment scales, inflammatory markers, blood ammonia, liver and renal function). Original reports and scans must be provided for verification by the study team.

8.1.4.3 Changes in HBsAg, HBeAg, and HBV DNA will be analyzed by comparing baseline and follow-up values.

8.2 Safety Objectives:

Observe the drug safety under different regimens

9 Adverse Event Recording

Adverse event (AE) is any unfavorable medical occurrence in a research participant, not necessarily having a causal relationship with the study. Serious adverse event (SAE) or reaction is any untoward medical occurrence that results in death, life-threatening, requiring or prolonging hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or an important medical event in the investigator’s judgment.

Expected AEs: As a observational real-world study that only collects clinical data and medical history without imposing additional procedures, visits, or costs, no extra risks are anticipated theoretically. However, obtaining consent and taking medical histories may cause psychological discomfort; investigators should therefore be careful with phrasing and patient communications.

Recording and management of AEs: If a patient experiences psychological discomfort during history taking, study staff should provide verbal reassurance and record the incident within 2 hours, notifying the designated study personnel. For patients showing persistent or severe psychological symptoms (e.g., depression, mania), psychiatric consultation and psychological support should be arranged within 12 hours, and the event recorded by designated personnel. For unexpected injuries or harms related to the study, appropriate treatment and compensation will be provided. All AEs observed during the study must be documented in detail. If SAEs occur, designated personnel will manage and record the event promptly and report to the ethics committee and relevant authorities within required timelines. Serious or unexpected adverse reactions not consistent with drug labeling will be reported to the hospital's pharmacovigilance/ADR monitoring department per relevant requirements.

10 Statistical Analysis Plan

Details of statistical methods and definitions of analysis datasets are provided in the separate Statistical Analysis Plan (SAP).

11 Data Management and Confidentiality

(1) Data Entry and Modification

Data entry and corrections are performed by investigators. All entered data must originate from source documents (e.g., original medical records, laboratory reports) and be consistent with original records. All observations and test results should be entered promptly, accurately, completely, clearly, and truthfully into case report forms and the electronic database. Data managers will review and manage entered data. For data queries, data managers will send queries to investigators, who should respond promptly; data managers may re-query if necessary.

(2) Confidentiality of Participant Information

All study participant information must be strictly confidential. Participant records and data will be identified by study ID numbers rather than names. Identifiable information will not be disclosed outside the study team without participant consent. All study staff are required to maintain confidentiality. Participant files will be stored in locked cabinets accessible only to authorized study personnel. To ensure regulatory compliance, government regulators or ethics committee members may inspect personal records at the study site per regulations. Any publications will not disclose participants' personal identifiers.

(3) Confidentiality of Study Data

Study data are confidential. Study staff must not disclose data to individuals outside the project without the principal investigator's authorization, nor transfer data to external institutions without hospital authorization. Transfer of human genetic resources or related data to foreign entities or domestic entities with foreign capital requires approval by the National Human Genetic Resources Administration; normal academic result publication that complies with regulations is permitted.

12 Quality Control and Assurance

The principal investigator will organize relevant training to ensure the study is conducted according to standards, and that case report forms and other documents comply with GCP principles and the protocol. All data and materials must be verifiable. Quality control will be applied at every study stage to ensure data reliability and correct execution of procedures. The principal investigator must ensure investigators adhere to the protocol, confirm data accuracy, and ensure completeness of reports and informed consent documentation prior to study initiation. Any protocol deviations should be reported to the ethics committee in a timely manner.

When necessary, the study team will develop standard operating procedures (SOPs) and implement quality control procedures throughout study conduct and data handling to ensure standardization and reliability.

13 Ethical Considerations

This observational study collects medical history and routine laboratory/imaging results and does not impose additional burden or costs on participants; therefore, it does not present additional theoretical risks. The study will be conducted after approval by the Huashan Hospital Ethics Committee and other relevant local ethics committees; participating sites must obtain approval from their own ethics committees prior to commencement. All eligible patients will sign informed consent forms. Participant information will be kept strictly confidential and recorded using study ID numbers rather than names. The study will be conducted in compliance with applicable national regulations (e.g., Measures for Ethical Review of Biomedical Research Involving Humans) and international ethical guidelines such as the Declaration of Helsinki. The Huashan Hospital Ethics Committee will perform continuing oversight of the study.

14 Recruitment and Informed Consent Process

Participants will be recruited from outpatient clinics and inpatient wards at participating centers when they are diagnosed with CHB. The study team will inform clinicians across relevant departments about recruitment criteria. Clinicians who identify eligible patients during routine

care will notify the study team. Study staff will then visit the patient, fully inform them of the study's risks and benefits, and obtain written informed consent.

15 Responsibilities of Participating Parties and Other Provisions

Responsibilities of lead site (Huashan Hospital):

1. Establish a standard operating procedure for the multicenter registry within the study, and define standards for each process (including enrollment criteria, database audit standards, and data statistical workflow); appoint database managers and quality control personnel to conduct regular checks on data entry quality and study progress at each site;
2. Coordinate data aggregation and analysis;
3. Assign personnel responsible for enrollment, follow-up, and data collection/recording at Huashan Hospital.

Sub-centers responsibilities:

Appoint personnel responsible for patient enrollment, follow-up, data collection, and record-keeping at each sub-center.

16 Reference

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