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# VIETNarms: a multi-arm trial of HCV treatment strategies in Vietnam

**Submission date**
12/09/2019

**Recruitment status**
No longer recruiting

**Registration date**
04/10/2019

**Overall study status**
Completed

**Last Edited**
12/05/2026

**Condition category**
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

## Plain English summary of protocol

Background and study aims:
Hepatitis C virus (HCV) is a virus that causes infection of the liver and can live in the body for long periods of time, often without causing symptoms. Over time (many years) the virus damages the liver by causing inflammation and scarring. Eventually, patients can develop liver failure and liver cancer.
New drugs to cure hepatitis C have become available in recent years. They can be taken by mouth, for shorter periods of time than previous treatments. They have fewer side-effects, and much better cure rates. Unfortunately, the tablets are expensive. This study is investigating ways of reducing the costs of curing hepatitis C, by comparing different tablet combinations and different treatment schedules.

Who can participate?
Adults who have had HCV infection for at least 6 months and are attending the outpatient hepatitis clinic at the Hospital for Tropical Diseases in Ho Chi Minh City.

What does the study involve?
The participants will be randomly allocated to receive different combinations of drugs that will be taken for different lengths of time. Everyone in this study will get a combination of tablets that has been shown to cure hepatitis C. The study will involve attending regularly clinical assessments at the Hospital for Tropical Diseases. The frequency and timing of visits depends on each study group. At each visit the patient will see the study doctors who will conduct a physical examination, ask questions about the participant's health and medications to assess the patients response to treatment, and perform blood tests needed for the study. This will include blood tests to check kidney and liver function, the level of virus in the blood, and the amount of DAA drugs in the blood.

What are the possible benefits and risks of participating?
The main benefit of participation is that most participants (over 19 out of 20) will be cured of hepatitis C, with most being cured on the first round of treatment or a second round if the first does not clear all the virus.
There are some common side effects associated with the study medicines. These include fatigue, headache, insomnia, dizziness, migraine, nausea, diarrhea, stomach ache, and pains in the

muscles and joints. There is also a small risk that the shorter courses of treatment might not cure the participant's hepatitis C and that their virus might become resistant to the drugs used, which might reduce the options for alternative treatments. The study involves several samples of blood being taken, which can be uncomfortable or painful and can produce bruising.

Where is the study run from?
University of Oxford (UK) through the Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City (Viet Nam)

When is the study starting and how long is it expected to run for?
November 2018 to December 2023

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
1. The main contact at Imperial College is Prof. Graham Cooke, g.cooke@imperial.ac.uk
2. The main contact at OUCRU is Prof. Jeremy Day
3. The main contact at the Hospital for Tropical Diseases is Dr. Nguyen Van Vinh Chau

# Contact information

### Type(s)
Scientific

### Contact name
Prof Graham Cooke

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# Additional identifiers

### Protocol serial number
35CN, 206296/Z/17/Z

# Study information

### Scientific Title

A strategic post-licensing trial of oral direct-acting antiviral hepatitis C treatment in VIETNam incorporating a novel design with multiple ARMS (VIETNARMS)

## Acronym
VIETNARMS

## Study objectives
1. Sofosbuvir/daclatasvir (SOF/DCV) and sofosbuvir/velpatasvir (SOF/VEL) based treatments are non-inferior to each other
2. Proposed direct-acting antiviral (DAA)-sparing strategies are non-inferior to standard fixed duration treatment
3. The addition of ribavirin to drug-sparing strategies makes them superior to ribavirin-free drug-sparing strategies

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
Current ethics approval as of 02/02/2022:
1. Approved 13/01/2020, Imperial College Research Ethics Committee (4th Floor, Faculty Building, Imperial College, London South Kensington Campus, London SW7 2AZ; +44 (0)207 594 1872; researchethicscommittee@imperial.ac.uk), ref: 18IC4919
2. Approved 24/09/2019, Ethical Evaluation Committee in Biomedical Research of Ministry of Health (No 138A Giang Vo St - Ba Đinh Dist, Hanoi, Vietnam), ref: 89/CN-HĐĐĐ
3. Approved 05/12/2019, Oxford Tropical Research Ethics Committee (University of Oxford Research Services, University Offices, Wellington Square, Oxford OX1 2JD; +44 (0)1865 282106; oxtrec@admin.ox.ac.uk), ref 9-19
4. Approved 10/07/2019, Hospital for Tropical Diseases Ethics Committee (764 Vo Van Kiet, Ward 1, District 5, Ho Chi Minh City, Vietnam), ref: 29/QĐ- BVBNĐ

Previous ethics approval:
1. Submitted 14/12/2018, Imperial College Research Ethics Committee (4th Floor, Faculty Building, Imperial College, London South Kensington Campus, London SW7 2AZ; researchethicscommittee@imperial.ac.uk)
2. Approved 06/09/2019, Ethical Evaluation Committee in Biomedical Research of Ministry of Health, Vietnam, ref: 89/CN-HĐĐĐ
3. Submitted 07/12/2018, Oxford Tropical Research Ethics Committee (University of Oxford Research Services, University Offices, Wellington Square, Oxford OX1 2JD; +44 (0)1865 282106; oxtrec@admin.ox.ac.uk), ref 9-19
4. Approved 10/07/2019, Hospital for Tropical Diseases Ethics Committee, Ho Chi Minh City, ref: 29/QĐ- BVBNĐ

## Study design
Multi-arm open-label randomised controlled trial

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Hepatitis C virus (HCV) infection

## Interventions
The study is focused on patients who have had hepatitis C virus (HCV) infection for more than 6 months. All potential participants will be identified for screening in the out-patient department of the Hospital for Tropical Diseases, Ho Chi Minh City. As part of their standard care, patients with suspected HCV infection will have routine laboratory tests, including full blood count, liver function tests, alpha-fetoprotein (AFP), liver ultrasound, fibroscan and HBsAg. These tests will be used to identify participants who may be suitable for screening.

The study is a parallel-group open-label factorial trial simultaneously addressing optimal direct-acting antiviral (DAA) regimen, treatment-shortening strategies, and the role of adjunctive ribavirin. Specifically each participant will be randomized factorially to:
1. Sofosbuvir/daclatasvir (SOF/DCV) versus sofosbuvir/velpatasvir (SOF/VEL) in a 1:1 ratio
2. Standard 12-week duration versus response-guided therapy (RGT) versus induction /maintenance versus PEG-interferon (PEG-IFN)/DAA ultra-short treatment in a 1:2:2:2 ratio to evaluate three strategies to achieve high cure rates with reduced drug treatment
3. Patients receiving the last 3 shortening strategies will be additionally randomized factorially to adjunctive ribavirin (RBV) or no RBV in a 1:1 ratio

Randomisation will be stratified by G6 versus all other HCV genotypes. The novel study design simultaneously evaluates many different aspects of treatment analogous to a multi-arm multistage (MAMS)/seamless Phase II/III design, accelerating the identification of the best strategies to put into practice, whilst enabling poorly performing approaches to be identified and dropped swiftly by regular monitoring.

All patients will receive 400 mg SOF and 60 mg DCV once daily or 400 mg SOF and 100 mg VEL once daily.

Those in the standard 12-week arm will receive 12 weeks of treatment, dispensed every 4 weeks. They will attend for visits at week 2, 4, 8, 12.

Those in the RGT arm will be dispensed 4 weeks of treatment at enrolment. A single quantitative viral load will be performed at a visit on Day 7 and treatment duration will determined by this viral load at the time of the Week 4 visit. Based on predicted kinetics, individuals with virus below the Lower Limit of Quantification (LLOQ) (12 IU/ml, Abbott assay or alternative equivalent) at Day 7 will be treated for 4 weeks, those with viral load between the LLOQ and 250 IU/ml will receive 8 weeks, with all others continuing for 12 weeks of total therapy. They will attend for visits at week 1, 4, 8 (if receiving ≥8 weeks treatment), and 12 (if receiving 12 weeks treatment). Drug will be dispensed every 4 weeks.

Those in the induction/maintenance arm will be dispensed 2 weeks of treatment and start standard daily therapy at enrolment. After 2 weeks, treatment will be administered on the basis of 5 days on, 2 days off with treatment breaks to coincide with the weekend. Participants will return to the clinic at 2 weeks, and will take the next following weekend off treatment, and all subsequent weekends off. They will attend for visits at Weeks 2, 4, 8 and 12, and drug will be dispensed at 2 and 8 weeks.

Those receiving ultrashort therapy with PEGylated interferon will receive additional weekly PEG-IFN for a total of 4 doses on Days 7, 14, 21 and 28. Drug will be administered at weekly clinic visits at Weeks 1, 2, 3, and 4.

Patients randomised to RBV will take ribavirin tablets for as long as they take DAA therapy i.e. for 4, 8 or 12 weeks in the RGT arm depending on viral load at Day 7, for 12 weeks in the induction/maintenance treatment arm (missing RBV doses on weekends off treatment), and 4 weeks in the ultra-short PEG-IFN/DAA treatment arm. The dose will be 1000 mg taken once daily with DAAs, with dose adjustment for renal impairment and anaemia if indicated.

## Intervention Type
Drug

## Phase
Phase II/III

## Drug/device/biological/vaccine name(s)
1. Sofosbuvir 2. Daclatasvir 3. Velpatasvir 4. Ribavirin 5. Pegylated interferon PEG-IFN

## Primary outcome(s)
Sustained Virological Response at 12 weeks (SVR12) defined as plasma HCV RNA persistently <LLOQ (lower limit of quantification) at 12 weeks after the end of first-line treatment, without prior failure. This is defined as an absence of virological failure up to and including 12 weeks after end of treatment, where failure is defined as either two consecutive measurements of HCV RNA >LLOQ (lower limit of quantification, <12 IU/ml, on Abbott assay or equivalent platform), taken at least 1 week apart, after two consecutive visits with HCV RNA <LLOQ, at any time during follow-up (during treatment or after finishing treatment), with the latter confirmatory measurement also being >2000 IU/ml, or two consecutive measurements of HCV RNA (taken at least 1 week apart) that are a 1 log10 increase above the HCV RNA nadir on treatment and >2000 IU/ml, at any time during follow-up (during treatment or after finishing treatment).

## Key secondary outcome(s))
1. Sustained virological response (SRV) after the end of the combined first treatment phase and any re-treatment phases (only applicable to mild patients), defined as per primary outcome measure
2. Lack of initial virological response in which measurements of HCV RNA (at any time, taken at least 1 week apart from baseline) are <1 log10 decrease in the HCV RNA load from baseline
3. All clinical grade 3 or 4 adverse events, serious adverse events, and all adverse reactions, recorded on the case report form from the start of the trial to 12 weeks after the end of treatment
4. Adverse events of any grade leading to change in treatment (SOF, DCV, VEL, RBV, PEG-IFN), recorded on the case report form from the start of the trial to 12 weeks after the end of treatment
5. Adverse reactions (any grade) (considered definitely/probably/possibly related to SOF, DCV, VEL, RBV, PEG-IFN), recorded on the case report form from the start of the trial to 12 weeks after the end of treatment
6. Emergence of resistance associated substitutions in individuals not achieving SVR12 assessed using viral sequencing of HCV taken at any time point.

## Completion date
31/12/2023

# Eligibility

### Key inclusion criteria
1. Aged ≥18 years
2. Prior evidence* of HCV infection for more than 6 months AND at least one detectable (>LLOQ) HCV viraemia within 60 days prior to the enrolment visit (by quantitative HCV RNA, qualitative assay or HCV genotype), with no subsequent undetectable results. This latter result may come from a sample taken at the screening visit.
3. Laboratory tests at the screening visit or within 60 days of enrolment/randomisation:
3.1. Creatinine clearance (estimated using Cockcroft-Gault) ≥50 ml/min
3.3. Haemoglobin >8.5 g/dl
4. Mild liver disease: No evidence of significant liver fibrosis resulting from any aetiology, defined as one of the following:
4.1. Fibroscan** score ≤9 kPa, equivalent to F0-F2, within 180 days prior to planned enrolment
4.2. Biopsy consistent with mild fibrosis (Ishak score ≤2/6) within 180 days prior to planned enrolment
5. HIV-uninfected or, if HIV-infected, stable on antiretroviral therapy for >6 months (not necessarily on same regimen throughout), with HIV viral load <50 copies/ml at the screening visit, and currently taking HIV treatment compatible with all possible trial treatment options (SOF/DCV +/- RBV and SOF/VEL +/-RBV), with no requirement for study drug dose adjustment
6. HBsAg negative or, if HBsAg positive, then stable on tenofovir-containing therapy***
7. Written informed consent obtained from the participant

* Evidence from clinical documentation, detected HCV antibody, HCV viraemia, qualitative viral RNA or HCV genotype.
** Fibroscan must be a valid result (based on at least 10 readings) performed by an experienced (as evidenced by CV and/or training logs) technician.
*** Participants co-infected with HCV and HBV fulfilling the standard criteria for HBV treatment and already commenced on treatment will continue to receive tenofovir treatment. Participants who are HBsAg positive but not requiring HBV treatment will commence tenofovir prophylaxis 1 week prior to DAA treatment, until 12 weeks after end of treatment, in keeping with EASL and local guidelines.

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Mixed

### Lower age limit
18 years

### Upper age limit
100 years

### Sex
All

## Total final enrolment
624

## Key exclusion criteria
1. No previous hepatitis C treatment failure with DAA based therapy
2. Unidentified HCV genotype after repeated sequencing attempts
3. Any condition in the judgement of the investigator which might limit the participant's life expectancy within the duration of the study (e.g. advanced hepatocellular carcinoma)
4. Any disorder or circumstance which in the opinion of the investigator may have a significant negative impact on the ability of the participant to adhere to the trial regimen
5. Disorder which may cause ongoing liver disease including, but not limited to, ongoing alcohol misuse
6. Currently receiving medication known to interact with study medications, for which avoidance of co-administration or dose adjustment for SOF, DCV, VEL, RBV or PEG-IFN, would be recommended in the Summary of Product Characteristics. This includes the antiretroviral (ARV) drugs efavirenz, atazanavir/ritonavir and zidovudine*.
7. Participants currently using amiodarone or digoxin (including participants with permanent pacemakers)
8. History of severe pre-existing cardiac disease, including unstable or uncontrolled heart disease, in the previous 6 months**
9. Abnormal ECG finding at screening in a participant with pre-existing mild-moderate cardiac disease that in the opinion of the investigator means they should not be enrolled
10. Any pre-existing condition that may be worsened by use of PEGylated-interferon, including deranged thyroid function***, autoimmune hepatitis, severe retinopathy**** and existence of, or history of severe psychiatric illness
11. Use of other investigational products in clinical studies within 60 days of screening
12. Pregnant or breastfeeding females, females planning pregnancy within 4 months of end of study, and males planning pregnancy with a female partner within 7 months of end of study

* HIV-infected individuals taking these medications may be included in the trial providing they can be switched to a suitable WHO-recommended ARV regimen. For example, efavirenz and atazanavir/ritonavir may be substituted with dolutegravir, raltegravir or lopinavir/ritonavir. Zidovudine may be substituted with tenofovir. Any switch should occur at least 1 month before randomisation, to ensure the new regimen is well-tolerated and the viral load remains suppressed. Participants requiring such a switch will continue on the new regimen for the duration of the trial. All ARV drug costs will be covered.
**Severe pre-existing cardiac disease defined as history of congestive heart failure, previous myocardial infarction, symptomatic angina in preceding 6 months, or life threatening arrhythmia (including complete heart block).
*** Participants with thyroid disease may be eligible providing any thyroid abnormalities (TSH, T4) are adequately controlled prior to initiation of treatment.
****All patients will undergo fundoscopy at screening by the study doctor. Patients with diagnosed or confirmed retinopathy at screening (including macular oedema, retinal artery or vein thrombosis, retinal haemorrhage, cotton wool spots, optic neuritis, papilloedema and retinal detachment) will be excluded from the trial if it is the opinion of the investigator that there is significant risk of this deteriorating if the patient were randomised to receive PEG-IFN.

## Date of first enrolment
01/12/2019

## Date of final enrolment

31/12/2022

# Locations

**Countries of recruitment**
Viet Nam

**Study participating centre**
**Oxford University Clinical Research Unit**
764 Vo Van Kiet
W.1
Dist.5
Ho Chi Minh City
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70000

**Study participating centre**
**Hospital for Tropical Diseases**
764 Vo Van Kiet
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# Sponsor information

**Organisation**
University of Oxford

**ROR**
https://ror.org/052gg0110

# Funder(s)

**Funder type**
Industry

**Funder Name**
Wellcome Trust

### Alternative Name(s)

### Funding Body Type
Private sector organisation

### Funding Body Subtype
International organizations

### Location
United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan
Clinical data and clinical laboratory data will be entered into CliRes, a Title 21 Code of Federal Regulations (CFR) Part 11-compliant data capture system provided by the OUCRU IT department. CRFs, and administrative documentation will be kept in a secure location and held for 15 years after the end of the trial so it can be available for future reference including audit. The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. This repository is housed by the OUCRU IT and Data management group on a secure server. Electronic data will be kept for at least 20 years at OUCRU.
In line with the Wellcome and MRC Policy and Guidance on Sharing of Research Data from Population and Patient Studies, results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within 6 months of the official date of final publication. The trial will follow the OUCRU data sharing policy, which is based on a controlled access approach based on the following principles:
1. No data should be released that would compromise an ongoing trial or study.
2. There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
3. Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.
Data will be available for sharing after the primary trial publication. Researchers wishing to access data should contact the Trial Management Group in the first instance.

### IPD sharing plan summary
Available on request

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | | 07/05/2025 | 12/05/2025 | Yes | No |
| Protocol article | | 18/05/2020 | 26/05/2020 | Yes | No |
| Other publications | Economic evaluation | 07/05/2026 | 12/05/2026 | Yes | No |