Allocating treatment resources for hepatitis C in the UK: a constrained optimization modelling approach

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ABSTRACT

Background and objective: Although the treatment of chronic hepatitis C (CHC) has significantly evolved with the introduction of direct-acting antivirals, the treatment uptake rates have been low especially among marginalized groups in the UK, such as people who inject drug (PWID) and men who have sex with men (MSM). Cutting health inequality is a major focus of healthcare agencies. This study aims to identify the optimal allocation of treatment budget for chronic hepatitis CHC among populations and treatments in the UK so that liver-related mortality in patients with CHC is minimized, given the constraint of treatment budget and equity issue.

Methods: A constrained optimization modelling of resource allocation for the treatment of CHC was developed in Excel from the perspective of the UK National Health System over a lifetime horizon. The model was designed with the objective function of minimizing liver-related deaths by varying the decision variables, representing the number of patients receiving each treatment (elbasvir-grazoprevir, ombitasvir-paritaprevir-ritonavir-dasabuvir, sofosbuvir-ledipasvir, and pegylated interferon-ribavirin) in each population (the general population, PWID, and MSM). Two main constraints were formulated including treatment budget and the issue of equity. The model was populated with UK local data applying linear programming and underwent internal and external validation. Scenario analyses were performed to assess the robustness of model results.

Results: Within the constraints of no additional funding over original spending in status quo and the consideration of the issue of equity among populations, the optimal allocation from the constrained optimization modelling (treating 13,122 PWID, 160 MSM, and 904 general patients with ombitasvir-paritaprevir-ritonavir-dasabuvir) was found to treat 2,430 more patients (relative change: 20.7%) and avert 78 liver-related deaths (relative change: 0.3%) compared with the current allocation. The number of patients receiving treatment increased 4,928 (relative change: 60.1%) among PWID and 42 (relative change: 35.8%) among MSM.

Conclusion: The current allocation of treatment budget for CHC is not optimal in the UK. More patients would be treated, and more liver-related deaths would be avoided using a new allocation from a constrained optimization modelling without incurring additional spending and considering the issue of equity.

Introduction

Hepatitis C, as a slowly progressing infectious disease arising from the hepatitis C virus (HCV), is of growing international concern due to the substantial burden of HCV-related morbidity and mortality [1–4]. During the two decades after infection, 27% of those with chronic HCV infection develop liver cirrhosis and 25% develop hepatocellular carcinoma [5,6]. Liver-related deaths due to decompensated cirrhosis and hepatocellular carcinoma, drug-related deaths due to drug overdose and suicide, and HIV-related deaths due to HCV and HIV co-infection are the three major groupings for mortality of chronic hepatitis C (CHC) [7]. Although the transmission of HCV infection worldwide has remained stable based on a declined prevalence, the number of patients with advanced liver diseases including decompensated cirrhosis and hepatocellular carcinoma are growing [8], which has posed a serious challenge for countries’ health spending and threaten the sustainability of funding for viral hepatitis elimination plans of the World Health Organization (WHO) [9].

In the UK (UK), an estimated 160,000 people are chronically infected with HCV [10], and 24,600 patients with a treatment episode in the NHS hepatitis C patients register were recorded in 2018 [11]. People who inject drug (PWID) and men who have sex with men (MSM) are the most at-risk populations, which are disproportionately...
affected by CHC in the UK [12,13]. PWID even contributed to more than 90% of new infections in 2016 [14]. As marginalized groups, PWID and MSM are generally not in routine clinical care [15] and report low treatment uptake rates ranging from 0.5% to 2.5% [16]. Preventing people from dying prematurely is the primary goal of the CHC care pathway defined by the UK National Health System (NHS) policies [17]. As informed by WHO targets, the All-Party Parliamentary Group (APPG) on Liver Health Inquiry in the UK has heard from patients, leading clinicians, NHS managers, senior pharmaceutical industry representatives, and national public health policy leads. The elimination of hepatitis C included a reduction in liver-related deaths, increased awareness of hepatitis C among PWID and MSM, a minimum of 20,000 new treatment initiations per year, proportional treatment targets to be sets for different populations, and universal access to treatment [18].

Injection-based pegylated interferon-ribavirin (PR) used to be the standard of care for CHC, lasted between 24 and 48 weeks, resulted in significant unpleasant side effects, and reported an overall sustained virus response (SVR) less than 50% [19]. The approach to treatment for CHC continues to evolve with the introduction of tablet-based direct-acting antivirals (DAAs) in Europe in 2015, lasting 8 to 12 weeks, resulting in few side effects and reporting an SVR upwards of 95% for all genotypes [20]. However, the high list prices of DAAs have led many countries and jurisdictions in Europe to restrict reimbursement only for the patient with advanced fibrosis, without drug or alcohol use, and with a specialist prescriber [21]. In the UK, despite the affordable deals on drug costs between NHS and industry and the economic value of increased treatment among PWID and MSM [22–24], a broader treatment funding distributed to PWID and MSM is often lost, and cutting health inequality is a major focus of the NHS plan [18]. Both government agencies and clinicians require evidence-based advice on the practical implementation of utilizing DAAs most efficiently.

Current resource allocation within health technology assessment (HTA) in the UK relies primarily on the cost-effectiveness analysis (CEA) and budget impact analysis (BIA). CEA typically ignores the constraints and barriers to implementation, including budget constraints, capacity constraints, issue of equity, and issue of ethics [25]. They are not flexible in allocating resources among different populations. BIA, however, only integrated the budget constraints in deliberations rather than in quantitative analysis. A constrained optimization modelling approach has been used to solve problems in many fields, such as allocation funding among different investments in financial planning, blending different crude oils to produce gasoline and logistics planning in the military [26]. In healthcare, constrained optimization modelling has been used for the purposes of capacity management, selection of facility location [27–29], development of optimal treatment algorithms [30], design of clinical trials [31], and optimal allocation of resources [32–39], whose value was further introduced by International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force on Constrained Optimization Methods [40,41]. However, most published constrained optimization studies are not transparent enough in constructing, solving, and reporting constrained optimization modelling and the applications of constrained optimization modelling have been slow [26]. Combining traditional economic evaluations with constrained optimization modelling, this study aims to identify the optimal allocation of budget to fund treatments for CHC among populations and treatments in the UK so that liver-related deaths in patients with CHC are minimized, given the constraint of treatment budget and other implementation barriers.

Methods

A constrained optimization modelling of resource allocation for the treatment of CHC was developed in Excel and to work in conjunction with an underlying core Markov model for CHC from the perspective of UK NHS over a lifetime horizon, following the guidance of Constrained Optimization Methods in Health Services Research from the ISPOR task force [40,41].

Problem structuring

According to the targets of elimination hepatitis C set by APPG in the UK, the constrained optimization modelling was designated with the objective function \( LD(X) \) of minimizing liver-related deaths by varying the decision variables \( X_{ij} \), representing the number of patients receiving each treatment \( j = 1, 2, 3, 4 \) in each population \( i = 1, 2, 3 \). The optimal patient distribution among treatments and population groups from the constrained optimization model was compared with the current status quo in the UK.

The four treatment strategies including elbasvir-grazoprevir (EVR/GRZ), ombitasvir-paritaprevir-ritonavir-dasabuvir (OBV/PTV/r), sofosbuvir-ledipasvir (SOF/LED) and the previous standard of care (PR) were analysed in the modelling. The three DAAs strategies were selected because they: 1) were recommended by the National Institute for Health and Care Excellence (NICE) for the same indication; and 2) were the predominant strategies utilised in the UK according to the NHS hepatitis...
C register. The comparative data on efficacy and safety and utilization distribution of four selected strategies were reported in the NICE network-meta-analysis [42] and treatment monitoring report from Public Health England [11], respectively. The general population, and two high-risk populations, including PWID and MSM in the UK were analysed in the modelling [43].

Two main constraints were formulated: treatment budget represented by B and issue of equity represented by E. The treatment budget constraint was the treatment spending in status quo in the UK, calculated as the sum of product of number of treated patients and total lifetime treatment costs in each population [10]. The equity constraint was examined based on the recommendation of proportional treatment for populations developed by APPG, which stated that each patient group could receive only the share of the overall treatment costs proportionate to its size of infected cases in the UK status quo [10,18].

The parameters of constrained optimization modelling included total lifetime costs per patient (TC) and liver-related death rates (TD) with each treatment or with no treatment in each population. The number of infected patients in each population was represented by Ni.

The liver-related deaths and the number of patients receiving each treatment from the optimal allocation were compared with the status quo of the treatment of CHC in the UK among the general population (1,223 with OBV/PTV/r; 718 with EBR/GRZ; 1,056 with SOF/LED; and 447 with PR), PWID (2,909 with OBV/PTV/r; 1,708 with EBR/GRZ; 2,513 with SOF/LED; and 1,064 with PR), and MSM (42 with OBV/PTV/r; 25 with EBR/GRZ; 36 with SOF/LED; and 15 with PR). In the current status quo, the number of patients receiving each treatment was calculated based on the number of treated patients among each population groups collected from the treatment monitoring report published by the Public Health England [11] and utilization distribution of four selected strategies derived from UK real-world evidence [44]. The liver-related deaths were simulated using the model.

Mathematical formulation

The mathematical problem was defined as follows:

Minimize

\[ LD(X) = \sum_{i=1}^{3} \left( \left( \sum_{j=1}^{4} TD_{ij}X_{ij} \right) + ND_{i} \left( N_{i} - \sum_{j=1}^{4} X_{ij} \right) \right) \]

Subject to

Budget constraint

\[ \sum_{i=1}^{3} \left( \left( \sum_{j=1}^{4} TC_{ij}X_{ij} \right) + NC \left( N_{i} - \sum_{j=1}^{4} X_{ij} \right) \right) \leq B \]

Issue of equity \( E : X_{ij} \propto N_{i} \)

\[ (i = 1, 2 \text{ and } 3 \text{ represents the general population, PWID and MSM, respectively}) \]

\[ (j = 1, 2 \text{ and } 3 \text{ and } 4 \text{ represents EBR/GRZ, OBV/PTV/r, SOF/LED and PR, respectively}) \]

\[ (\propto : \text{inproportionto}) \]

Model development

The development of the constrained optimization modelling for CHC treatment consists of programming the mathematical problem and obtaining the input parameters to estimate objective function and constraints. Linear programming was applied based on one critical condition that a linear incremental change in the independent variable, namely decision variable, and constraint, results in a linear incremental change in the dependent output, namely objective function [38,45]. The programming was developed in Microsoft Excel Solver [32,39,46,47]. In the absence of comparative data on clinical and cost outcomes between PWID/MSM and the general population from long-term follow-up studies to populate the programming, a core Markov model [48–50] widely used with many local adaptations [51–61] for evaluating the chronic progression and treatment of CHC was further adapted to compare clinical and cost outcomes of CHC treatment among different populations in the UK setting. The structure of the core Markov model (Figures 1) was kept as reported in the previous study [62]. Population-specific input including mortality, reinfection, and HRQoL was added in the core model. The local population-specific data was derived from a systematic review of economic evaluation models for the treatment of CHC [62] and extensive reviews of the epidemiologic burden of CHC among the general and high-risk populations [1–4]. The outcomes of the core Markov model including total lifetime treatment costs per patient and liver-related death rates with each strategy and without any treatment in each population were embedded in the constrained optimization programming to determine the optimal allocation.

Patients enter the model with chronic HCV (F0-F3) or compensated cirrhosis (F4) defined by Metavir score and receive pharmacological treatment for CHC. Patients could transit to the next stage of severity (decompensated cirrhosis and hepatocellular carcinoma) and require liver transplants (different health states between the first year and subsequent years). Patients could die at
Fig. 1. The core Markov model structure.
any time according to the UK general mortality and increased mortalities due to advanced liver complications were considered. Recovered patients could get reinfected, leading patients back from the recovered states to chronic HCV states.

The input for the general population (Additional file 1.1) was obtained from Johnson et al. [63] and NICE committee paper [42], including input of baseline characteristics, transition probabilities, clinical efficacy in terms of SVR, health states utilities, and treatment costs consisting of drug costs, treatment monitoring costs, treatment costs of drug-related adverse events and medical treatment costs of different health states.

The input for PWID and MSM was kept identical to that for the general population except for input of mortality, reinfection and utility among PWID, and input of reinfection and utility among MSM (Table 1). An increased mortality due to overdose [64], a higher reinfection rate due to high-risk behaviour including needle sharing [65,66], and lower HRQoL due to substance use [67–70] were considered among PWID. A higher reinfection rate due to high-risk sexual activities and network characteristics [15,71,72] and lower HRQoL due to poorer mental health and psychological problems [70,73–75] were considered among MSM.

All costs were inflated to the year 2019. Cost and health outcomes were discounted at a 3.5% annual rate based on the UK guidelines [76].

Model validation

Two types of validation were applied to the constrained optimization modelling using linear programming to ensure that appropriate techniques motivated by real-world observations were employed [77]: internal validation and external validation. The conceptualization of the decision problem, model structure, data sources, assumptions, coding, and results were validated by an independent analyst with a pre-defined checklist. The cost and clinical outcomes from the core Markov model were compared with those from the other UK models [48–50,63].

Scenario analysis

Two scenario analyses were performed to assess the robustness of model results, by: 1) changing the objective function from minimization of liver-related deaths to maximization of quality-adjusted life-years (QALYs) gained and adopting only budget constraint. Then the results of optimal allocation were compared with those of ICER-based priority applied by NICE; 2) investigating the minimum additional funding required to treat at least 20,000 people every year to reach the HCV elimination target in the UK, as suggested by APPG.

Results

Parameters derived from the core Markov model

The total lifetime treatment costs per patient with CHC and liver-related death rates with each strategy and without any treatment, derived from the core Markov model, are presented in Table 2. The detailed cost outcomes and other clinical outcomes are shown in Additional file 1.2.

The total lifetime treatment costs per patient with each strategy among three populations ranged from a lower value set of £44,991 (OBV/PTV/r), £48,272 (EBR/GRZ), £50,321 (SOF/LED), and £66,613 (PR) among the general population, to a median value set of £45,483 (OBV/PTV/r), £48,660 (EBR/GRZ), £50,815 (SOF/LED), and £63,852 (PR) among PWID, then to a higher value set of £50,396 (OBV/PTV/r), £53,587 (EBR/GRZ), £55,736 (SOF/LED), and £68,718 (PR).
among MSM. The total lifetime treatment costs per patient without any treatment among three populations were incurred by the medical treatment costs of different health states of CHC and ranged from £27,850 among PWID to £32,769 among MSM and the general population.

The liver-related death rates with each strategy among three populations ranged from a lower value set of 15.96% (OBV/PTV/r), 15.89% (EBR/GRZ), 15.88% (SOF/LED), and 18.37% (PR) among PWID, to a median value set of 18.38% (OBV/PTV/r), 18.31% (EBR/GRZ), 18.28% (SOF/LED), and 21.37% (PR) among the general population, then to a higher value set of 19.27% (OBV/PTV/r), 19.22% (EBR/GRZ), 19.20% (SOF/LED), and 21.92% (PR) among MSM. The liver-related death rates without any treatment among three populations ranged from 19.16% among PWID to 22.98% among MSM and the general population.

### Optimal allocation of treatment resources in the base case

The optimal allocation of resources for the treatment of CHC using constrained optimization modelling is presented in Table 3, which summarized the decision variables and objective function in the optimal allocation and the comparison with the current status quo in the UK.

Within the constraints of no additional funding over original spending in status quo and the consideration of the issue of equity among populations, the optimal allocation from the constrained optimization modelling (treating 13,122 PWID, 160 MSM, and 904 the general patients with OBV/PTV/r) was found to treat 2,430 more patients (relative change: 20.7%) and avert 78 liver-related deaths (relative change: 0.3%) compared with the current allocation. The number of patients receiving treatment increased 4,928 (relative change: 60.1%) among PWID and 42 (relative change: 35.8%) among MSM.

#### Model validation

The conceptualization of the decision problem was based on the clinical practice of CHC treatment and validated by a health economics expert (S.A.). The specification and value of parameters in constrained optimization modelling were selected based on the UK real-world evidence [8,10,18,66,78–81] identified by extensive reviews [1–4] and derived from the core Markov model in the UK setting populated with UK local data identified by the systematic review [62]. The numbers of liver-related deaths estimated

### Table 2. Parameters derived from the core Markov model.

|                  | The general population | PWID | MSM |
|------------------|------------------------|------|-----|
| Total lifetime treatment costs |                         |      |     |
| OBV/PTV/r        | £44,991                | £45,483 | £50,396 |
| EBR/GRZ          | £48,272                | £48,660 | £53,587 |
| SOF/LED          | £50,321                | £50,815 | £55,736 |
| PR               | £66,613                | £63,852 | £68,718 |
| No treatment     | £32,769                | £27,850 | £32,769 |
| Liver-related death rates |                     |      |     |
| OBV/PTV/r        | 18.38%                 | 15.96% | 19.27% |
| EBR/GRZ          | 18.31%                 | 15.89% | 19.22% |
| SOF/LED          | 18.28%                 | 15.88% | 19.20% |
| PR               | 21.73%                 | 18.37% | 21.92% |
| No treatment     | 22.98%                 | 19.16% | 22.98% |

DAAs: direct acting antivirals; EBR/GRZ: elbasvir-grazoprevir; MSM: men who have sex with men; OBV/PTV/r: ombitasvir-paritaprevir-ritonavir-dasabuvir; PR: pegylated interferon-ribavirin; PWID: people who inject drugs; SOF/LED: sofosbuvir-ledipasvir

### Table 3. Optimal allocation of treatment resources for CHC in the base case.

| Decision variables (Number of patients receiving treatment) | Objective function (Minimum number of liver-related death) |
|------------------------------------------------------------|-----------------------------------------------------------|
| The general population                                    |                                                          |
| OBV/PTV/r                                                  |                                                          |
| EBR/GRZ                                                    |                                                          |
| SOF/LED                                                    |                                                          |
| PR                                                        |                                                          |
| PWID                                                       |                                                          |
| EBR/GRZ                                                    |                                                          |
| SOF/LED                                                    |                                                          |
| PR                                                        |                                                          |
| MSM                                                       |                                                          |
| EBR/GRZ                                                    |                                                          |
| SOF/LED                                                    |                                                          |
| PR                                                        |                                                          |
| Current allocation                                         |                                                          |
| 1,223 718 1,056 447                                         | 2,909 1,708 2,513 1,064 160 25 36 15 30,730              |
| Optimal allocation                                         |                                                          |
| 904 0 0 13,122                                              | 0 0 0 0 0 0 0 0 0 0 0 30,651                              |

EBR/GRZ: elbasvir-grazoprevir; MSM: men who have sex with men; OBV/PTV/r: ombitasvir-paritaprevir-ritonavir-dasabuvir; PR: pegylated interferon-ribavirin; PWID: people who inject drugs; SOF/LED: sofosbuvir-ledipasvir
by this model are consistent with those currently observed in the UK [82].

**Scenario analysis**

In the first scenario of maximizing QALY within the constraint of no additional funding and without the consideration of the issue of equity, the allocation results from the constrained optimization model were the same as the standard allocation from the ICER-based priority (Table 4). Compared with no treatment, OBV/PTV/r treatment among the general patients was found to lead to the lowest ICER value among the three populations. Optimal allocation (treatment 20,066 the general patients with OBV/PTV/r) was found to treat 5,880 more patients (relative change: 41.4%), increase 17,303 more QALYs gained (relative change: 1.3%) compared with the base case optimal allocation. The change of objective function from the minimization of liver-related deaths to the maximization of QALYs gained did not impact the optimal allocation in this case, but the change of constraint did.

In the second scenario, increasing the funding by 2.1% with the consideration of the issue of equity was found to raise the overall number of patients receiving treatment to 20,000 to reach the HCV elimination target, as suggested by APPG recommendation (Table 5).

**Discussion**

This study showed that even without additional funding over original spending and within the constraint of equity in resource allocation among populations, the optimal allocation from the constrained optimization modelling could treat more patients and avert more liver-related deaths compared with the status quo of treating CHC patients in the UK.

**Implementation of constrained optimization modelling**

The value of constrained optimization modelling in resource allocation has been introduced by several studies. Juusola et al. [39] developed a linear resource allocation model alongside the traditional static CEA to determine the optimal mix of HIV treatment and prevention so that QALYs gained and HIV infections averted were maximized, given a fixed budget. In accordance with our analyses of liver-related deaths and QALYs gained, the choice of objective function did not change the optimal resource allocation. However, the approximating diminishing with linear objective function in Jessie et al. analyses could lead to a less accurate estimate. Lasry et al. [38] developed a nonlinear allocation model alongside the epidemic model to apport HIV prevention resources among interventions and populations so that HIV incidence was minimized, given a fixed budget. However, the structure of the epidemic model of HIV did not include the stratification of geography, age, and race. It did not report the type of behavior change intervention, which weaken its impact on dictating healthcare resource allocation. Demartea et al. [32] developed a linear allocation model alongside the Markov model to identify the mix of cervical cancer prevention strategies so that the cancer cases were minimized, given a fixed budget. In line with our results of ICER-based scenario analysis, Demartea et al. reported that when only considering budget constraints, the resource

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**Table 4. Optimal allocation in the scenario of ICER-based analysis.**

| Decision variables (Number of patients receiving treatment) | Objective function (Maximum number of QALYs gained) |
|-------------------------------------------------------------|-----------------------------------------------------|
| The general population                                      |                                                    |
| OBV/PTV/GRZ/SOF/LEDFPR                                     |                                                    |
| Current allocation                                          | 1,223                                               |
| Base case optimal allocation                                | 904                                                 |
| Scenario case optimal allocation                            | 20,066                                              |
| ICER versus no treatment                                    | 7,945                                               |
|                                                            | £10,220£11,371£72,410£19,282£23,080£25,029£155,730£16,197|

**Table 5.**

| Decision variables (Number of patients receiving treatment) | Objective function (Maximum number of QALYs gained) |
|-------------------------------------------------------------|-----------------------------------------------------|
| The general population                                      |                                                    |
| OBV/PTV/GRZ/SOF/LEDFPR                                     |                                                    |
| Current allocation                                          | 1,223                                               |
| Base case optimal allocation                                | 904                                                 |
| Scenario case optimal allocation                            | 20,066                                              |
| ICER versus no treatment                                    | 7,945                                               |
|                                                            | £10,220£11,371£72,410£19,282£23,080£25,029£155,730£16,197|
allocation of a constrained optimization model obtained the same results as that of a CEA with ICER-based priority. However, the static Markov model could not be accounted for the dynamic effect of vaccination on infection, such as herd protection, and the constrained optimization modelling could not address equity problems. Earnshaw et al. [33] developed a linear allocation model alongside the Markov model to select sets of interventions so that the QALYs gained of patients with type II diabetes were maximized, given budget and equity constraints. However, only drug costs were included in the model.

Constrained optimization modelling has been also applied in hepatitis C. Busschots et al. [47] developed a constrained optimization modelling in Excel to demonstrate the number of HCV patient need to treat per year to reach the WHO targets for HCV elimination in Belgium, given the constraints of the number of known HCV patients, annual HCV incidence and the number of years until the year 2030 is reached. However, no specific treatment or prevention interventions were incorporated in the model. Chhatwal et al. [83] developed a Markov microsimulation model to inform the optimal timing of HCV treatment for patients on the liver transplant waiting list. However, only two scenarios were compared, treatment on the waiting list versus treatment after the liver transplant, which made the term ‘optimal’ loosely used and made the analysis closer to a traditional CEA.

Despite the potential value of constrained optimization modeling, the implementation in healthcare has been slow and not been based on evidence that demonstrates the optimal solution in a mathematical sense.

**Added value of this optimization modelling**

Constrained optimization modeling is an emerging tool to expand the comparison of different allocations of resources across population groups. Rather than the comparison of one health technology versus another health technology in a traditional CEA and BIA, the optimization approach expands across various technologies and across population groups. Equitable patient access was addressed in this constrained optimization modelling to integrate the health equity between the general population and marginalised high-risk populations. The impact of reinfection on treatment outcomes and lower HSUs in among marginalised high-risk populations were addressed, which were not always considered in the limited CEAs among PWID [84,85] and MSM [24].

Constrained optimization modeling is a flexible tool to solve different decision problems based on a simple yet accurate framework. It can be either embedded with traditional models or populated with data directly from literature. Although there are four treatments among three different population groups in our analysis, the structure of the decision problem is still straightforward. The simplicity of constrained optimization modelling design in Excel allows it to be adapted easily and used for different types of decision problems, such as determining the mix of interventions and populations and investigating the additional funding need in our analyses. Furthermore, constrained optimization modelling could be applied in determining the timing to initiate treatment [86] and the price of health technologies [45], which could not readily be included in a traditional CEA or BIA.

In our analysis, the objective of finding optimal distribution of treatment budget to minimize the liver-related deaths in CHC patients requires decisions different from those typically made in a CEA or BIA. What’s more, our analysis addressed public health problems with minor reformulations: 1) what is the effect of considering equity issue between population groups; and 2) how much increased funding is needed to reach a specific target, which cannot be answered in a CEA or BIA.
Constrained optimization modelling is a practically implementable tool to solve the context-specific problem. It allows the decision-makers to set a variety of constraints reflecting local conditions, such as limited budget, limited coverage rates, limited capacity, and measure of equity, for deciding a particular problem. Data from the national treatment monitoring database in the UK were derived to populate the modelling. The early data in the register suggest that PWID and MSM are starting to be identified via local and outreach services. As more data become available, linking these data to targeting allocation of resources for treating patients would improve equity of access to treatment and inform the progress of eliminating hepatitis C in the UK. Common resource allocation methodologies including cost-effectiveness ranking and net-benefit analysis [87] cannot provide quantitative information for policymakers about how to allocate funds among the interventions and population groups and how many extra funds are still needed to reach specific public health targets and cannot include equity or other implementation constraints. Our analyses of the base case and different scenarios can help policymakers allocate limited funds and decide the amount of additional funding and reveal the acceptable levels of costs and health outcomes to trade-off for equity consideration.

Limitations of this optimization analysis

Only the general population and high-risk populations including PWID and MSM were analysed in constrained optimization modelling. The other at-risk populations in the UK [12] included prisoners, immigrants, commercial sex workers, homeless people, and haemodialysis patients. The prisoners and immigrants were another contribution subgroup to hepatitis C. According to the statistics from the Ministry of Justice in 2018 [88], the total number of prisoners in the UK was 83,123. The estimated range of HCV seroprevalence in prisoners was from 1.3%-19.2% [43], and 32% of prisoners reported drug use history [89]. The relatively high HCV seroprevalence among prisoners is caused by a high population of PWID in prison and unsafe injecting and tattooing taking place within prison. There is also a high seroprevalence of HCV within some South Asian (ranging from 0.0% to 9.6%) and Eastern European (ranging from 3.1%-9.3%) immigrants due to a high risk of infection from unsafe medical and dental care or unsterile shaving and barber’s equipment [43]. The accurate estimates on the overlap between PWID and prisoners or immigrants were not clear due to the lack of data. However, the population subgroups in the analysis covered more than 90% of CHC patient in the UK, including the general population (n = 66,000), PWID (n = 119,850) and MSM (n = 1,800) [90].

Besides treatment initiatives to lead to a decline in liver-related deaths and in overall prevalence, the care pathway for hepatitis C spans the entire range of interventions from preventing, testing, and linking to care. Harm reduction including needle and syringe provision (NSP) and opioid substitution treatment (OST) was recognised as a key strategy for PWID to prevent transmission. Similarly, protected sexual behaviour campaigns and education about transmission risks are crucial for MSM. The indirect effect of ‘treatment as prevention’ was not considered in this analysis. The effect of prevention interventions, however, have been investigated in other dynamic transmission models among PWID [91–97] and MSM [98,99].

Given limited comparative data between the general population and high-risk populations including PWID and MSM, a set of assumptions was made in the core Markov model. The non-AIDS mortality in MSM was used as the proxy of HCV-mono-infected MSM, which was not significantly different compared with that in the general norm (hazard ratio:0.61, p = 0.440) according to an observational cohort study conducted in Spain [100]. A clinical trial conducted in the UK reported that the increased disease progression of CHC was associated with male gender, old age, and alcohol assumption greater than 40 units per week [101]. To our knowledge, however, no studies confirmed the accelerated liver disease progression among PWID and MSM. Therefore, a conservative assumption of identical transition probability was used in the model. A poorer HRQoL among PWID [67,68,70] and MSM [70,73–75] compared to the population norm was reported in many qualitative humanistic burden studies. However, no utility elicitation studies reported the comparative differences from hepatitis C patients. An adjustment of 0.8 for health states utility values (HSUVs) of PWID used by several CEAs [69,102] was applied and a conservative assumption of adjustment of 0.9 for HSUVs of MSM was made in the scenario analysis of ICER-based priority. However, the main objective function in the base case was to minimize liver-related deaths and the choice of the objective function in our analysis did not change the resource allocation.

This analysis only partially addressed the equity issue, which considered that all populations could be reached with identical treatment uptake rates. In this case, the constrained optimization modelling tended to maximize the treatment uptake rates among high-risk populations, which were not always included in routine clinical practice. It also considered each population as homogeneous. However, with added information, the modelling could be adapted to take into account
regional disparities, such as differences in epidemiology, contact rate, healthcare capacity, and costs in large countries with diverse regional health settings.

The constraint of capability, such as healthcare practitioners and laboratory equipment, was not considered in the modelling. However, aligned with WHO targets, the delivery of treatment of CHC in the UK has been expanded in the community facilities without referral to specialist care [18]. With the ease of dispensing treatment in the community, all general practitioners could be accredited to deliver treatment with less spending. Old PR treatment requires sophisticated laboratory capacity to diagnose the presence of chronic infection, the viral genotype, and assess the degree of liver fibrosis. Combinations of DAAs treatments, however, are effective against all genotypes and much safer than PR, thus preventing the need for genotyping and reducing the complexity of monitoring for adverse events.

**Recommendations for future studies**

Given the study results, the generation of new clinical studies for the treatment efficacy of DAAs among PWID and MSM with CHC are suggested. The gold standard of a clinical study is the double-blinded randomized controlled trial RCT. Typical RCTs of DAAs for CHC included the general patients with serum positive for HCV and excluded patients with other causes for the liver disease other than CHC and substance abuse [103]. The stigma surrounding hepatitis C within MSM communities was reported as significantly higher than stigma surrounding HIV [18]. Including PWID and MSM in the clinical trial and following up with them to complete the full treatment protocol could be difficult but meaningful to get information about viral kinetics and treatment outcome by performing key comparisons between PWID/MSM and the general patients. In this case, HSUVs for CHC of PWID and MSM could be collected alongside the trial to generate patient preference-related evidence which is not only commonly used in a typical CEA, but also could be used in constrained optimization modelling.

The indirect effect of ‘treatment as prevention’ is suggested to be expanded. The future model could simulate the movement of PWID through different injecting durations, prevention intervention states, and injecting risk [92]. Stratifications by injecting duration, and ex-injecting drug users, could capture the higher rates of injecting cessation during the first few years of injecting and the varying death rates according to the different injecting duration categories. Stratifications by different prevention intervention states, such as no intervention, on OST only, on NSP only, and both OST and NSP, could capture the different compliance to intervention, which may have an impact on treatment discontinuation. Stratifications by high and low injecting risk, with high-risk being defined as being homeless and/or a crack cocaine injector that has been shown to increase the risk of HCV infection acquisition among PWID, which results in more benefit of ‘treatment as prevention’. The future model could simulate the movement of MSM through different interaction behaviour with sexual partnerships [104], HIV pre-exposure prophylaxis states, and HIV infection status [105]. Stratifications by sexual partnerships could include ‘regular partnerships’ (relationships lasting more than one time step), ‘casual partnerships’ (individuals who meet up with for casual sex on more than one occasion), and ‘random partnerships’ (individuals who meet up with for only a single interaction) to capture different sexual risk and the potential compliance to treatment.

The inequities in the treatment of CHC root in the multiple social and structural factors including HCV stigma, housing, access to social and welfare supports, access to employment and income, and CHC treatment delivery system [106]. Treatment alone is not enough to eradicate HCV and the inequities in CHC testing and treatment also need to be addressed to achieve hepatitis C elimination targets. The evidence for case-finding and linkage to care was summarized by Public Health England to support decision-making on prioritisation of resources [107]. The integrated resource allocation covering the whole care pathway of CHC is suggested from awareness-raise, prevention, testing, diagnosis, treatment, to monitoring.

The detailed process of the model validation for the constrained optimization modelling is suggested in further studies of constrained optimization modelling. Demarteau et al. [32] and Juuola et al. [39] reported the validation of optimization analyses by only investigating the impact of changing the value of key parameters on model results. The future optimization model should be valid for all possible combinations of decision variables as suggested by the ISPOR guidelines [40].

**Conclusion**

The current allocation of treatment budget for CHC is not optimal in the UK. More patients would be treated and more liver-related deaths would be avoided using a new allocation from a constrained optimization modelling without incurring additional spending and considering the issue of equity.

**Disclosure statement**

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Author contribution
All authors contributed to study conception and design. Ru Han contributed to the model construction, acquisition of data, analysis and interpretation of data and first draft of the manuscript. Samuel Abella and Shuyao Liang contributed to the model validation. Clément François and contributed to critical revision of the manuscript for important intellectual content. Clément François and Mondher Toumi contributed to supervision of the study. All authors read and approved the final manuscript.

Data availability statement
The data relating to the model parameters are all included in the article and/or its supplementary materials. The model used in the study can be made available to researchers upon request.

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