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## Trends in clinical development timeframes for anti-viral drugs launched in the UK, 1981-2014

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**Trends in clinical development timeframes for anti-viral drugs launched in the UK, 1981-2014**

Derek J Ward[1], Edward Hammond[1], Luan Linden-Phillips[1], Andrew J Stevens[2]

1.    NIHR Horizon Scanning Research & Intelligence Centre,

      School of Health and Population Sciences, University of Birmingham, Edgbaston,

      Birmingham, B15 2TT, United Kingdom

2.    Department of Public Health, Epidemiology and Biostatistics,

      School of Health and Population Sciences, University of Birmingham, Edgbaston,

      Birmingham, B15 2TT, United Kingdom

**Corresponding author:**

Dr Derek Ward d.j.ward@bham.ac.uk

## Abstract

**Objectives:** Recent decades have witnessed the development of highly innovative new anti-viral drug therapies. However, there are concerns that rising costs and lengthening development times could have implications for future patient access to innovative new drugs. We sought to establish whether the time taken for the clinical development of new anti-viral drugs in the UK had increased since the 1980s.

**Design and setting:** Retrospective observational study of all new anti-viral drugs licensed for use in the UK.

**Primary and secondary outcome measures:** Duration of clinical development (from initiation of studies in humans to receipt of Marketing Authorisation), subdivided into clinical trial and regulatory approval periods by the date of Marketing Authorisation Application.

**Results:** 48 new anti-viral drugs were licensed for use in the UK between 1981 and 2014 (inclusive), over half (54%) initially for HIV infection. The overall mean duration of clinical development was 77.2 months, of which 64.6 months was spent in clinical trials before regulatory submission. The total time in clinical development increased from 41.7 months for drugs licensed 1981-1992 to 91.7 months for drugs licensed 2004-2014. This increase was accounted for by an increase in the clinical trials period and not the regulatory approval period, for which there was no observable trend. Drugs initially licensed to treat hepatitis C had a longer duration of clinical development than those indicated for other viral infections. However, the, initially shorter clinical development durations of drugs indicated for HIV infection increased more rapidly across the study period than those indicated for other viral infections.

**Conclusions:** The time spent by anti-viral drugs in clinical development has increased markedly in recent decades despite many initiatives to speed access to innovative new drugs. However, this represents only one part of the translational research pathway, and a complete picture of development timeframes is lacking.

## Article summary

**Strengths and limitations of this study**

- This is the most up to date and complete study that considers trends in clinical development timelines for new drugs introduced into the UK.

- The study used data from the European Medicines Agency, Medicines and Healthcare Products Regulatory Agency, and British National Formulary to ensure that all relevant drugs were identified and regulatory dates were accurate.

- However, this study considered only the clinical phase of development, from the initiation of clinical trials to regulatory approval, and omits the time and resources needed for discovery and preclinical development, as well as post-authorisation activities.

- This study did not consider new indications or the repurposing of existing licensed and marketed drugs.

## Introduction

Recent decades have seen the emergence and identification of several new viral infections of global significance,[1][2] but they have also witnessed the development of highly innovative new anti-viral drug therapies, which have, for example, dramatically improved the prognosis of those infected with Human Immunodeficiency Virus (HIV)[3] and now are radically changing the care of those infected by hepatitis C.[4] However, concerns have been expressed about the increasing costs of developing new drugs and bringing them into clinical use.[5-9] In broad terms, drug development begins with discovery and pre-clinical laboratory research, before moving on to clinical development, starting with first testing in humans (phase I clinical trials) and continuing until regulatory review and approval.[5][6][10][11] Phase I to III clinical trials may be responsible for more than half the time and cost required to bring a new drug from discovery to regulatory approval.[6][12] Therefore, trends in the time taken for clinical development may be an important driver of increasing total development costs as well as having implications for patient access to innovative new medicines.

A number of authors have attempted to characterise the time taken to translate basic research findings into clinical practice; a review by Morris *et al*[10] identified a number of studies reporting the time taken to translate health research, concluding that 17 years was the most likely estimate despite wide variation in definitions, and marked differences in the time periods studied and approaches to data collection. However, few researchers have considered trends in drug development timeframes. Keyhani *et al*[13] considered the time taken from the Investigational New Drug (IND) Application (a step required by the US Food and Drug Administration (FDA) prior to testing in humans[14]) to the filing of a New Drug Application[15] and subsequent FDA approval (the latter time points representing the regulatory review process). For all new drugs approved in the USA from 1992-2001, the authors found no increase in the time taken to conduct clinical trials prior to filing a New Drug Application (median 5.1 years) and a decrease in the time taken for the subsequent regulatory review and approval. Kaitin and DiMasi[16] considered a much longer time

frame (1980-2009) and also found a decrease in time taken for regulatory review by the FDA.

However, they found an increase in the clinical trial periods prior to filing (increasing from a mean

5.7 years for drugs approved in the USA 1980-1984, to 6.4 years for those approved 2005-2009) and

concluded that this was due, in part, to increasing numbers of central nervous system and anti-

neoplastic agents with very long average development times. However, the clinical trial periods prior

to filing (i.e. from IND application to filing a New Drug Application) for HIV anti-viral agents also

increased from a mean 2.3 to 5.0 years, and clinical trial periods for other anti-infective agents

(including other anti-viral drugs) increased from 4.2 to 6.6 years. More recent data on drug

intervention trials registered with ClinicalTrials.gov suggests that trial lengths may have reduced in

recent years (from 2.0 years for trials beginning in 2005 to 1.3 years for those beginning in 2009),

but this trend was considerably less marked for industry sponsored trials, which are more likely to

support the approval of new drugs.[17]

Similar data on trends in drug development have not been published for the UK. We sought to

determine whether the overall time taken for the clinical development (clinical trial periods prior to

filing and subsequent consideration by the regulator) of new drugs launched in the UK had changed

over more than three decades, using data for anti-viral drugs.

## Methods

All new drugs first licensed for use in the UK between 1981 and 2014 (inclusive) and specifically

indicated for the treatment of viral disease were identified along with their initial approved

indication(s) from relevant editions of the British National Formulary (BNF) and the European

Medicines Agency (EMA) website. The BNF lists all preparations available for prescribing and/or

dispensing in the UK, including prescription only and over-the-counter medicines. A new drug was

defined as a new chemical entity or new biological product not previously licensed for use in the UK;

new formulations and new indications for existing licensed drugs were omitted from the study, as

were new combination products where all the active components were already licensed and

available separately or in other combination products.

Clinical development was defined as the period from the initiation of studies in humans (clinical

trials) to the receipt of a Marketing Authorisation (MA or 'licence') applicable to the UK from the

Medicines and Healthcare Products Regulatory Agency (MHRA) or the EMA as appropriate.[5] This

period was further sub-divided by the date of Marketing Authorisation Application (MAA, regulatory

submission or 'filing') into periods representing clinical trials (prior to filing) and subsequent

regulatory approval. The initiation of clinical development was determined from searches of a

commercial pharmaceutical R&D database (Pharmaprojects, Informa Group plc) and a bibliographic

database of published biomedical literature (Medline, US National Library of Medicine). The date of

IND Application to the FDA was taken as the start of clinical development; where this was not

available, the first report of clinical trials (typically phase I) was used instead. The dates of MAA and

MA were obtained from the EMA website or direct from the MHRA.

The duration of clinical development, as well as the clinical trial and regulatory approval periods,

were calculated to the nearest month. Simple descriptive statistics were used to summarise these

data and explore differences in durations according to the drug indication (viral disease) and year of

licence (1981-1992, 1993-2003 and 2004-2014). The statistical significance of differences in mean

duration were determined using unpaired t-tests. Scatter plots were used to visualise trends in

development timeframes by year of UK drug launch, and where relevant, Pearson's correlation

coefficient and least-squares linear regression lines were calculated. Statistical analyses were

conducted using SPSS (v21.0, IBM).

## Results

There were 48 new drugs licensed for the treatment of viral diseases in the UK during the 34 year period from 1981 to 2014, representing a mean 1.4 new drugs per year (Table 1). Almost half of these drugs were licensed in the middle period (1993-2003, 48%), while just 15% were licensed in the earlier period (1981-1992). Over half of new drugs (54%) were initially indicated for HIV infection. The next most frequent initial indication was hepatitis C infection (15%), followed by infection with cytomegalovirus (13%), hepatitis B (8%), herpes simplex virus (4%), influenza virus (4%), and respiratory syncytial virus (2%, full details provided in supplementary file 1).

The overall mean duration of clinical development was 77.2 months, the majority of which was spent in clinical trials before the date of regulatory submission (84%, Table 1). The total time in clinical development increased during the study period, from 58.0 months for drugs licensed 1981-1992, to 91.7 for drugs licensed 2004-2014, a result that was statistically significant (p=0.048). This increase was accounted for by an increase in time spent in clinical trials before regulatory submission, which increased from 41.7 months for drugs licensed 1981-1992 to 78.4 months for drugs licensed 2001-2014 (p=0.027). No equivalent increase in time spend in the regulatory approval period was observed. A statistically significant upward linear trend in the total duration of clinical development (r=0.31, y=1.26 x year − 2442.01, p=0.034, Figure 1) and the clinical trials period (r=0.34, y=1.38 x year − 2695.37, p=0.018) was observed for drugs licensed across the whole study period, suggesting that mean total clinical development and clinical trial durations increased by twelve months every 9.5 and 8.7 year period, respectively. In contrast, no significant linear trend was observed for the duration of the regulatory approval period (r=0.16, y= −0.12 x year + 253.36, p=0.32).

Considering the initial indications for new drugs, those licensed to treat hepatitis C infection had a longer duration of clinical development than those indicated for HIV infection or other viral infections (Table 1), though this result was not statistically significant. A statistically significant

upward linear trend was observed for total clinical development durations for drugs first licensed to treat HIV across the study period (r=0.54, y=1.84 x year – 3606.44, Figure 2). The clinical development durations of drugs initially licensed to treat other viral infections increased at a slower rate, and the trend was not statistically significant (r=0.29, y=0.98 x year –1882.40).

## Discussion

We have shown that for drugs licensed in the UK to treat viral infections, the time spent in clinical development has increased markedly over the last three decades. This increase is due to increasing time spent in clinical trials before regulatory submission; no trend was observed in the time taken for regulatory approval. In addition, drugs licensed for hepatitis C appeared to spend longer in development than those for other viral infections but clinical development durations increased more rapidly for drugs licensed to treat HIV than those licensed to treat other viral infections. Our estimate of the rate of increase in clinical development times is greater than that found by Kaitin and DiMasi for drugs approved in the USA up to 2009.[16] However, our estimates of the total clinical development time and clinical trial periods prior to filing was lower than their reported estimates for HIV anti-viral drugs (4.8 years and 4.0 years, respectively), potentially indicating earlier application to and approval by the US regulator.

This study relied on data from the BNF, MHRA and EMA, ensuring that the identification of drugs was comprehensive and the data on regulatory dates were accurate. For initiation of clinical trials, we relied on the date of IND application, a process which only applies to the USA and not to Europe. This point in the development of a new molecule occurs when the developer "wants to test its diagnostic or therapeutic potential in humans".[14] On a global basis, the IND application may be regarded as a reasonable proxy for the decision to advance development of a new drug beyond pre-clinical testing given that in recent decades the majority of new drugs have been launched in the USA at an earlier or similar time to Europe.[18] The European Union (EU) equivalent process, requiring

submission of a request for authorisation of clinical trials, stems from a 2001 Directive[19] and is

therefore a more recent development that could not be applied to the study period of interest. We

could not determine a date for IND application in six cases (representing drugs launched between

1982 and 1996). The association between clinical development time and year of launch was

maintained after excluding these drugs from the analysis (r=0.42, y=1.99 x year – 3912.46, p=0.006).

Our study addresses only the clinical development period of drug development; it omits the time

and resources needed to discover and bring a candidate molecule through laboratory and initial

animal studies, and does not consider activities post-approval, including marketing, phase IV studies,

evidence reviews and the generation of guidance to clinicians and health services.[6 11 20] Several

commentators have described models of the translation pathway providing consistent definitions for

different stages of the process and allowing comparison between studies and evaluation of efforts to

reduce unwarranted delays. Trochim et al[11] proposed a "process marker" model that recognises

translational research as a continuous process that may be "bidirectional, variable, [and] complex"

with observable milestones along a generalised pathway allowing measurement of time elapsed

between them. Others have built on this approach to create a generalisable model for all healthcare

innovation, recognising that the process marker model may be more appropriate to technology

driven developments.[20] Hanney et al propose a matrix of four different "tracks" in the innovation

process, building from discovery research, through human research and research review, to clinical

and health service/public policy development, and finally clinical practice.[20] This recognises the

overlapping nature of research translation activities, and allows for the initiation of different tracks

at different times despite relevant research still occurring in 'earlier' tracks. Our study considers the

'Clinical Trials System' element of the translational research continuum described by Trochim et al[11]

and overlapping elements of tracks 2 and 3 in Hanney et al's description of the innovation process.[20]

Taken together, these help identify drivers of the trends seen. In this way, the increasing demands of

regulators that have led to increasing complexity of clinical trial programmes are highly relevant to

the increase in clinical trial periods we have observed. This has been recognised by policy-makers, who have agreed revisions to the 2001 EU Clinical Trials Directive (effective from 2004), widely seen as having a negative impact on translational research, increasing administrative burdens and waiting periods,[21-24] and introduced a range of initiatives in the USA and Europe to provide a more rapid pathway to approval for innovative drugs that address serious conditions, urgent public health needs, or specific patient groups.[25 26]
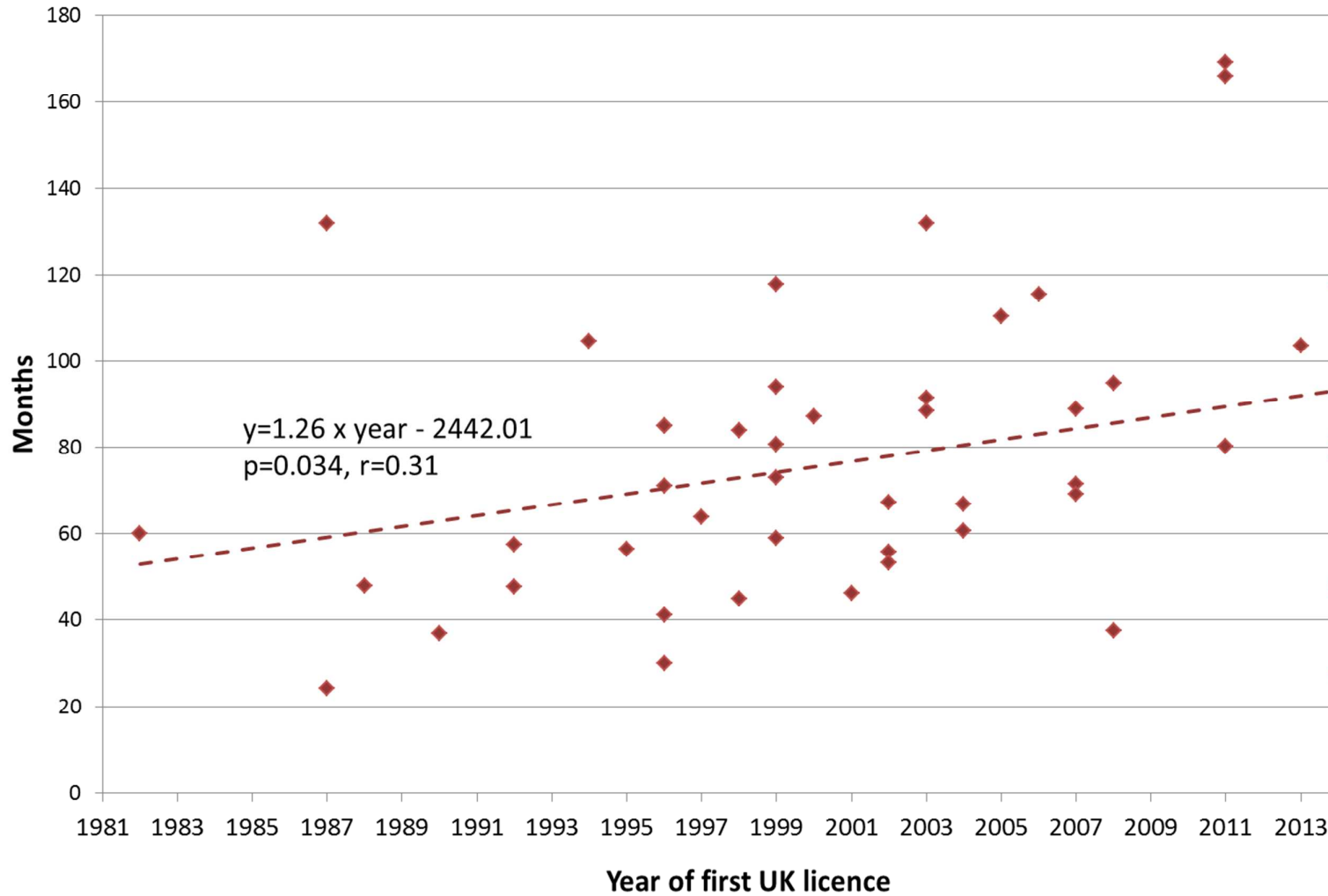
Despite the introduction of these initiatives, visual inspection of our data (Figures 1 and 2) shows no apparent step change consistent with a sudden change in the regulatory environment (such as the creation of the EMA, originally known as the European Agency for the Evaluation of Medicinal Products, or implementation of the EU Clinical Trials Directive). This may be expected given the long lead times for planning and conducting clinical trial programmes, though further analysis shows no association between the duration of clinical development and the year when clinical development commenced ($r=0.04$, $y= -0.16 + 399.67$, $p=0.80$). However, the impact of regulators can be seen in the shorter development durations seen for HIV drugs, which have previously been reported as receiving Marketing Authorisation without "large-scale human clinical trials",[27] though our data suggest this difference is now lessening. This is an example of regulators responding to a public health need and being willing to adopt a different view of the risk-benefit in specific circumstances.[20] One current regulatory development applicable to the UK is the MHRA's Early Access to Medicines Scheme, which allows patients with serious conditions to access medicines that have not yet been approved where there is a clear unmet medical need.[28] This will not necessarily accelerate clinical development as measured by our study metrics (time to Marketing Authorisation), but it may facilitate collection of real-world data to support earlier adoption of innovative new drugs. In this way it has parallels with the EMA's adaptive licensing pilot, but this EU-wide initiative also has the potential to bring forward the date of a drugs initial Marketing Authorisation, allowing first approval in highly selected patient populations based on more limited initial clinical studies.[29] Both these

examples are indicative of a wider move towards early dialogue between regulators and commercial developers,[26] a move which is mirrored by health technology assessment (HTA) agencies in Europe, either alone or in parallel with regulators.[26 30] Early dialogue may or may not lead to a reduction in clinical development durations, but it is likely to be reflected in the design and conduct of late-phase clinical trial programmes.[30 31] This will have an uncertain effect on clinical trial times if HTA agencies demand longer-term patient-related outcomes rather than proxy measures on which to judge value, but it may be expected to speed up the total time to adoption and diffusion of those drugs judged to be most clinically and cost-effective.

The past few decades have seen the introduction of many novel anti-viral drugs, but the time spent in clinical development before drug approval has increased substantially. We found no evidence that this trend in increasing clinical development timescales is levelling off, though many of the current initiatives aimed to speed access to innovative new medicines are too recent to have affected clinical trial programmes for drugs launched up to 2014, and will therefore require further evaluation in the coming years. However, it is important to stress that adequate time spent in clinical trials is critical to generate evidence of safety, efficacy and cost-effectiveness,[20] and that regulators require adequate time to consider this evidence and strike an appropriate balance between benefit and risk.[32] There are necessarily limits to clinical development durations, but this is only one part of the whole discovery to clinical practice translational pathway, and increased time in one part of the pathway may be offset by gains elsewhere. Further research should incorporate measures of pre-clinical and adoption timeframes in order to gain a complete picture and ensure there are no unwarranted delays in novel drugs reaching patients in need.

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**Figure 1. Duration of clinical development for anti-viral drugs by year of first licence in the UK, 1981-2014.**



$y = 1.26 \times year - 2442.01$
$p = 0.034, r = 0.31$

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**Figure 2. Duration of clinical development for anti-viral drugs indicated for HIV and other viral infections by year of first licence in the UK, 1981-2014.**



Legend:
- Indicated for HIV infection
- Indicated for other viral infections

y=0.98 x year - 1882.40
p=0.29, r=0.24

y=1.84 x year - 3606.44
p=0.004, r=0.54

Y-axis: Months
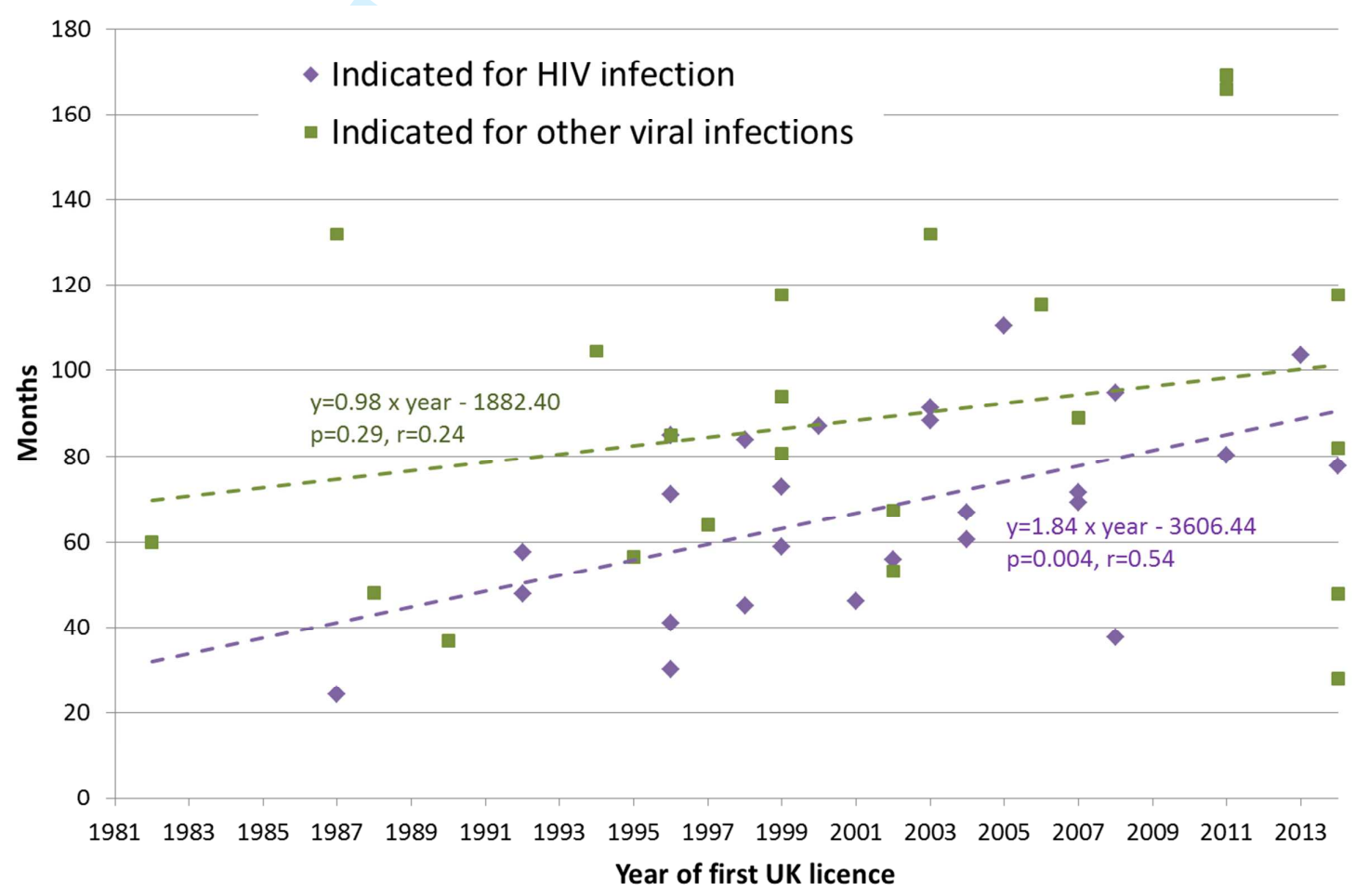X-axis: Year of first UK licence

**Table 1. Duration of clinical development for anti-viral drugs, in total and sub-divided into clinical trials and regulatory approval periods, by year of first licence and indication in the UK, 1981-2014.**

| | Number | Duration of development (months) | | | | | | | | | | | |
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| | | Clinical trials period | | | | Regulatory approval period | | | | Total duration | | | |
| | | Mean | SE | 95% CI | | Mean | SE | 95% CI | | Mean | SE | 95% CI | |
| All new drugs | 48 | 64.6 | 4.70 | 55.9 to | 73.3 | 12.6 | 0.96 | 10.8 to | 14.7 | 77.2 | 4.75 | 68.7 to | 86.6 |
| Drugs licensed between | | | | | | | | | | | | | |
|    1981-1992 | 7 | 41.7 | 9.90 | 23.5 to | 62.6 | 16.3 | 5.02 | 7.3 to | 26.8 | 58.0 | 13.2 | 37.6 to | 86.4 |
|    1993-2003 | 23 | 63.2 | 5.34 | 53.6 to | 73.7 | 11.2 | 1.01 | 9.3 to | 13.1 | 74.4 | 5.21 | 64.9 to | 84.9 |
|    2004-2014 | 17 | 78.4 | 9.02 | 61.5 to | 96.7 | 13.3 | 1.10 | 11.3 to | 15.6 | 91.7 | 8.80 | 75.2 to | 108.9 |
| Initial licensed indication | | | | | | | | | | | | | |
|    HIV infection | 26 | 55.8 | 4.18 | 47.5 to | 64.1 | 11.8 | 0.94 | 10.0 to | 13.5 | 67.6 | 4.43 | 58.7 to | 76.5 |
|    Hepatitis C infection | 7 | 92.1 | 20.52 | 52.8 to | 133.4 | 13.9 | 4.69 | 8.4 to | 25.2 | 106.0 | 21.00 | 63.7 to | 147.2 |
|    Other viral infection | 15 | 66.8 | 7.97 | 51.2 to | 83.3 | 13.5 | 1.59 | 10.3 to | 16.4 | 80.3 | 7.32 | 66.6 to | 95.3 |

## Contribution of the authors

DJW and AJS conceived the original study idea, and EH and LL-P contributed to the development of the study design and methods. EH collected the data and carried out the analysis with assistance from LL-P and DJW. All authors (DJW, EH, LL-P and AJS) were involved in the interpretation of the results. DJW produced the initial draft of the paper, which was then circulated repeatedly to all authors for critical revision. DJW, EH, LL-P and AJS read and approved the final version. All authors had full access to all of the study data (including statistical reports and tables), and can take responsibility for the integrity of the data and the accuracy of the analysis. DJW is the guarantor.

## Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors have financial support from the National Institute for Health Research (NIHR) for the submitted work; all authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and all authors have no other relationships or activities that could appear to have influenced the submitted work.

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## Data sharing statement

The dataset used for analyses has been provided as a supplementary file, and will also be added to

the Dryad repository, which will provide a permanent, citable and open access home for the dataset.

No additional unpublished data are available.

## References

1. Satcher D. Emerging Infections: Getting Ahead of the Curve. Emerging Infectious Disease. March 1995; 1(1).

2. Marston HD, Folkers GK, Morens DM, et al. Emerging Viral Diseases: Confronting Threats with New Technologies. Science Translational Medicine 2014;**6**(253):ps10.

3. Hogg R, Lima V, Sterne JA, et al. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;**372**(9635):293-9.

4. Sheridan C. FDA approvals usher in the post-interferon era in HCV. Nature Biotechnology 2014;**32**(1):3-5.

5. House of Commons Select Committee on Health. The Influence of the Pharmaceutical Industry. London: House of Commons, 2005.

6. Mestre-Ferrandiz J, Sussex J, Towse A. The R&D cost of a new medicine. London: Office of Health Economics, 2012.

7. Scannell JW, Blanckley A, Boldon H, et al. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 2012;**11**(3):191-200.

8. Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov 2011;**10**(6):428-38.

9. Hay M, Thomas DW, Craighead JL, et al. Clinical development success rates for investigational drugs. Nature Biotechnology 2014;**32**(1):40-51.

10. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. Journal of the Royal Society of Medicine 2011;**104**:510-20.

11. Trochim W, Kane C, Graham MJ, et al. Evaluating Translational Research: A Process Marker Model. Clinical and Translational Science 2011;**4**(3):153-62.

12. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 2010;**9**(3):203-14.

13. Keyhani S, Diener-West M, Powe N. Are development times for pharmaceuticals increasing or decreasing? Health Affairs 2006;**25**(2):461-68.

14. US Food and Drug Administration. Investigational New Drug (IND) Application. Last update 27/10/2015. http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm. Accessed 16/06/2015.

15. US Food and Drug Administration. New Drug Application (NDA). Last update 02/03/2015. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm. Accessed 16/06/2015.

16. Kaitin KI, DiMasi JA. Pharmaceutical Innovation in the 21st Century: New Drug Approvals in the First Decade, 2000-2009. Clinical Pharmacology & Therapeutics 2011;**89**(2):183-88.

17. Pregelj L, Verreynne M, Hine D. Changes in clinical trial length. Nat Rev Drug Discov 2015;**14**(5):307-08.

18. Downing NS, Aminawung JA, Shah ND, et al. Regulatory Review of Novel Therapeutics — Comparison of Three Regulatory Agencies. New England Journal of Medicine 2012;**366**(24):2284-93.

19. European Commission. Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1). 2010. C82/01. http://ec.europa.eu/health/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf.

20. Hanney SR, Castle-Clarke S, Grant J, et al. How long does biomedical research take? Studying the time taken between biomedical and health research and its translation into products, policy, and practice. Health Research Policy and Systems 2015;**13**(1):1.

21. Frewer LJ, Coles D, Champion K, et al. Has the European Clinical Trials Directive been a success? BMJ 2010;**340**:c1862.

22. Gulland A. Number of global clinical trials done in UK fell by two thirds after EU directive. BMJ 2009;**338**:b1052.

23. Hartmann M. Impact assessment of the European Clinical Trials Directive: a longitudinal, prospective, observational study analyzing patterns and trends in clinical drug trial applications submitted since 2001 to regulatory agencies in six EU countries. Trials 2012;**13**:53.

24. Watson R. EU nations approve law to overhaul clinical trials. BMJ 2013;**347**:f7682.

25. Baird LG, Banken R, Eichler HG, et al. Accelerated Access to Innovative Medicines for Patients in Need. Clinical Pharmacology & Therapeutics 2014;**96**(5):559-71.

26. Grainger D. Is this the real life? Is this just fantasy? International Journal of Technology Assessment in Health Care 2014;**30**(03):239-40.

27. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really $802 million? Health Affairs 2006;**25**(2):420-28.

28. Medicines and Healthcare Products Regulatory Agency. Apply for the early access to medicines scheme (EAMS). https://www.gov.uk/apply-for-the-early-access-to-medicines-scheme-eams#overview. Accessed 16/06/2015.

29. Eichler HG, Baird LG, Barker R, et al. From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients. Clinical Pharmacology & Therapeutics 2015;**97**(3):234-46.

30. Jönsson B. Bringing in health technology assessment and cost-effectiveness considerations at an early stage of drug development. Molecular Oncology 2015;**9**(5):1025-33.

31. Mestre-Ferrandiz J, Deverka P, Pistollato M, et al. The current drug development paradigm: responding to US and European demands for evidence of comparative effectiveness and relative effectiveness. Occasional Paper. London: Office for Health Economics, 2014.

32. Tominaga T, Asahina Y, Uyama Y, et al. Regulatory Science as a Bridge Between Science and

Society. Clinical Pharmacology & Therapeutics 2011;**90**(1):29-31.

## Supplementary data file:

**Anti-viral drugs licenced for use in the UK, 1981-2014 with key development dates and initial licensed indication.**

| Drug name | Investigational New Drug (IND) Application (or first report of clinical trial where IND not known) | Date of Marketing Authorisation Application to EMA or MHRA | Date Marketing Authorisation granted for the UK | Initial licensed indication (viral infection) |
|---|---|---|---|---|
| Abacavir | Jun-93 | Jun-98 | Jul-99 | Human Immunodeficiency Virus |
| Aciclovir | (1977) | Jun-81 | Jun-82 | Herpes Simplex Virus |
| Adefovir dipivoxil | Mar-92 | Mar-02 | Mar-03 | Hepatitis B |
| Amprenavir | Jul-93 | Oct-98 | Oct-00 | Human Immunodeficiency Virus |
| Atazanavir | Aug-98 | Apr-02 | Mar-04 | Human Immunodeficiency Virus |
| Boceprevir | Sep-97 | Nov-10 | Jul-11 | Hepatitis C |
| Cidofovir | Mar-92 | Dec-95 | Jul-97 | Cytomegalovirus |
| Daclatasvir | Oct-07 | Dec-13 | Aug-14 | Hepatitis C |
| Darunavir | Mar-01 | Jan-06 | Feb-07 | Human Immunodeficiency Virus |
| Didanosine | Jun-88 | Jun-91 | Jun-92 | Human Immunodeficiency Virus |
| Dolutegravir | Jul-07 | Dec-12 | Jan-14 | Human Immunodeficiency Virus |
| Efavirenz | Jun-94 | Jun-98 | May-99 | Human Immunodeficiency Virus |
| Elvitegravir | Mar-05 | May-12 | Nov-13 | Human Immunodeficiency Virus |
| Emtricitabine | Jun-96 | Dec-02 | Oct-03 | Human Immunodeficiency Virus |
| Enfuvirtide | Oct-95 | Sep-02 | May-03 | Human Immunodeficiency Virus |
| Entecavir | Nov-96 | Sep-04 | Jun-06 | Hepatitis B |
| Etravirine | Oct-00 | Jul-07 | Aug-08 | Human Immunodeficiency Virus |
| Famciclovir | (1985) | Nov-93 | Feb-94 | Herpes Simplex Virus |
| Fomivirsen | Nov-92 | May-98 | Aug-99 | Cytomegalovirus |
| Fosamprenavir | Jun-99 | Dec-02 | Jul-04 | Human Immunodeficiency Virus |
| Foscarnet sodium | Jan-87 | Dec-87 | Feb-90 | Cytomegalovirus |

| Ganciclovir | (1984) | Jun-87 | Jun-88 | Cytomegalovirus |
|---|---|---|---|---|
| Indinavir sulphate | Jul-93 | Mar-96 | Dec-96 | Human Immunodeficiency Virus |
| Lamivudine | Aug-89 | Jun-95 | Sep-96 | Hepatitis B |
| Ledipasvir | Jul-12 | Feb-14 | Nov-14 | Hepatitis C |
| Lopinavir | May-97 | Jun-00 | Mar-01 | Human Immunodeficiency Virus |
| Maraviroc | Dec-01 | Dec-06 | Sep-07 | Human Immunodeficiency Virus |
| Nelfinavir | Jun-94 | Feb-97 | Mar-98 | Human Immunodeficiency Virus |
| Nevirapine | Apr-91 | Jun-97 | Apr-98 | Human Immunodeficiency Virus |
| Oseltamivir | Nov-96 | Feb-01 | Jun-02 | Influenza |
| Palivizumab | Oct-91 | Jul-98 | Aug-99 | Respiratory Syncytial Virus |
| Raltegravir | Nov-04 | Apr-07 | Jan-08 | Human Immunodeficiency Virus |
| Ribavirin | (1976) | Dec-83 | Jun-87 | Hepatitis C |
| Rilpivirine | Mar-05 | Sep-10 | Nov-11 | Human Immunodeficiency Virus |
| Ritonavir | May-94 | Feb-96 | Nov-96 | Human Immunodeficiency Virus |
| Saquinavir | Mar-90 | Sep-95 | Feb-96 | Human Immunodeficiency Virus |
| Simeprevir | Jul-04 | Apr-13 | May-14 | Hepatitis C |
| Sofosbuvir | Jan-10 | Apr-13 | Jan-14 | Hepatitis C |
| Stavudine | (Jun-1989) | Jul-95 | Jul-96 | Human Immunodeficiency Virus |
| Telaprevir | Aug-97 | Dec-10 | Sep-11 | Hepatitis C |
| Telbivudine | Dec-99 | Feb-06 | Apr-07 | Hepatitis B |
| Tenofovir disoproxil fumarate | Jun-97 | May-01 | Feb-02 | Human Immunodeficiency Virus |
| Tipranavir | Aug-96 | Nov-04 | Oct-05 | Human Immunodeficiency Virus |
| Valaciclovir | Mar-91 | Aug-94 | Nov-95 | Cytomegalovirus |
| Valganciclovir | Oct-97 | Nov-01 | Mar-02 | Cytomegalovirus |
| Zalcitabine | (Sep-89) | Feb-92 | Jun-92 | Human Immunodeficiency Virus |
| Zanamivir | Aug-89 | Jan-99 | Jun-99 | Influenza |
| Zidovudine | Jul-85 | Jan-87 | Jul-87 | Human Immunodeficiency Virus |

# BMJ Open

## Trends in clinical development timeframes for anti-viral drugs launched in the UK, 1981-2014: a retrospective observational study

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**Trends in clinical development timeframes for anti-viral drugs launched in the UK, 1981-2014: a retrospective observational study**

Derek J Ward[1], Edward Hammond[1], Luan Linden-Phillips[1], Andrew J Stevens[2]

1.      NIHR Horizon Scanning Research & Intelligence Centre,

        School of Health and Population Sciences, University of Birmingham, Edgbaston,

        Birmingham, B15 2TT, United Kingdom

2.      Department of Public Health, Epidemiology and Biostatistics,

        School of Health and Population Sciences, University of Birmingham, Edgbaston,

        Birmingham, B15 2TT, United Kingdom

**Corresponding author:**

Dr Derek Ward d.j.ward@bham.ac.uk

## Abstract

**Objectives:** Recent decades have witnessed the development of highly innovative new anti-viral drug therapies. However, there are concerns that rising costs and lengthening development times could have implications for future patient access to innovative new drugs. We sought to establish whether the time taken for the clinical development of new anti-viral drugs launched in the UK had increased since the 1980s.

**Design and setting:** Retrospective observational study of all new anti-viral drugs licensed for use in the UK.

**Primary and secondary outcome measures:** Duration of clinical development (from initiation of studies in humans to receipt of Marketing Authorisation), subdivided into clinical trial and regulatory approval periods by the date of Marketing Authorisation Application.

**Results:** 48 new anti-viral drugs were licensed for use in the UK between 1981 and 2014 (inclusive), over half (54%) initially for HIV infection. The overall mean duration of clinical development was 77.2 months, of which 64.6 months was spent in clinical trials before regulatory submission. The total time in clinical development increased from 41.7 months for drugs licensed 1981-1992 to 91.7 months for drugs licensed 2004-2014. This increase was accounted for by an increase in the clinical trials period and not the regulatory approval period, for which there was no observable trend. Drugs initially licensed to treat hepatitis C had a longer duration of clinical development than those indicated for other viral infections. However, the, initially shorter clinical development durations of drugs indicated for HIV infection increased more rapidly across the study period than those indicated for other viral infections.

**Conclusions:** The time spent by anti-viral drugs in clinical development has increased markedly in recent decades despite many initiatives to speed access to innovative new drugs. However, this represents only one part of the translational research pathway, and a complete picture of development timeframes is lacking.

## Article summary

**Strengths and limitations of this study**

- This is the most up to date and complete study that considers trends in clinical development timelines for new drugs introduced into the UK.

- The study used data from the European Medicines Agency, Medicines and Healthcare Products Regulatory Agency, and British National Formulary to ensure that all relevant drugs were identified and regulatory dates were accurate.

- However, this study considered only the clinical phase of development, from the initiation of clinical trials to regulatory approval, and omits the time and resources needed for discovery and preclinical development, as well as post-authorisation activities.

- This study did not consider new indications or the repurposing of existing licensed and marketed drugs.

## Introduction

Recent decades have seen the emergence and identification of several new viral infections of global

significance,[1][2] but they have also witnessed the development of highly innovative new anti-viral

drug therapies, which have, for example, dramatically improved the prognosis of those infected with

Human Immunodeficiency Virus (HIV)[3] and now are radically changing the care of those infected by

hepatitis C.[4] However, concerns have been expressed about the increasing costs of developing new

drugs and bringing them into clinical use.[5-9] In broad terms, drug development begins with discovery

and pre-clinical laboratory research, before moving on to clinical development, starting with first

testing in humans (phase I clinical trials) and continuing until regulatory review and approval.[5][6][10][11]

Phase I to III clinical trials may be responsible for more than half the time and cost required to bring

a new drug from discovery to regulatory approval.[6][12] Therefore, trends in the time taken for clinical

development may be an important driver of increasing total development costs as well as having

implications for patient access to innovative new medicines.

A number of authors have attempted to characterise the time taken to translate basic research

findings into clinical practice; a review by Morris *et al*[10] identified a number of studies reporting the

time taken to translate health research, concluding that 17 years was the most likely estimate

despite wide variation in definitions, and marked differences in the time periods studied and

approaches to data collection. However, few researchers have considered trends in drug

development timeframes.  Keyhani *et al*[13] considered the time taken from the Investigational New

Drug (IND) Application (a step required by the US Food and Drug Administration (FDA) prior to

testing in humans[14]) to the filing of a New Drug Application[15] and subsequent FDA approval (the

latter time points representing the regulatory review process). For all new drugs approved in the

USA from 1992-2001, the authors found no increase in the time taken to conduct clinical trials prior

to filing a New Drug Application (median 5.1 years) and a decrease in the time taken for the

subsequent regulatory review and approval. Kaitin and DiMasi[16] considered a much longer time

frame (1980-2009) and also found a decrease in time taken for regulatory review by the FDA. However, they found an increase in the clinical trial periods prior to filing (increasing from a mean 5.7 years for drugs approved in the USA 1980-1984, to 6.4 years for those approved 2005-2009) and concluded that this was due, in part, to increasing numbers of central nervous system and anti-neoplastic agents with very long average development times. However, the clinical trial periods prior to filing (i.e. from IND application to filing a New Drug Application) for HIV anti-viral agents also increased from a mean 2.3 to 5.0 years, and clinical trial periods for other anti-infective agents (including other anti-viral drugs) increased from 4.2 to 6.6 years. More recent data on drug intervention trials registered with ClinicalTrials.gov suggests that trial lengths may have reduced in recent years (from 2.0 years for trials beginning in 2005 to 1.3 years for those beginning in 2009), but this trend was considerably less marked for industry sponsored trials, which are more likely to support the approval of new drugs.[17]

Similar data on trends in drug development have not been published for drugs launched in the UK. We sought to determine whether the overall time taken for the clinical development (clinical trial periods prior to filing and subsequent consideration by the regulator) of new drugs launched in the UK had changed over more than three decades, using data for anti-viral drugs.

## Methods

All new drugs first licensed for use in the UK between 1981 and 2014 (inclusive) and specifically indicated for the treatment of viral disease were identified along with their initial approved indication(s) from relevant editions of the British National Formulary (BNF) and the European Medicines Agency (EMA) website. The BNF lists all preparations available for prescribing and/or dispensing in the UK, including prescription only and over-the-counter medicines. A new drug was defined as a new chemical entity or new biological product not previously licensed for use in the UK; new formulations and new indications for existing licensed drugs were omitted from the study, as

were new combination products where all the active components were already licensed and available separately or in other combination products.

Clinical development was defined as the period from the initiation of studies in humans (clinical trials) to the receipt of a Marketing Authorisation (MA or 'licence') applicable to the UK from the Medicines and Healthcare Products Regulatory Agency (MHRA) or the EMA as appropriate.[5] This period was further sub-divided by the date of Marketing Authorisation Application (MAA, regulatory submission or 'filing') into periods representing clinical trials (prior to filing) and subsequent regulatory approval. The initiation of clinical development was determined from searches of a commercial pharmaceutical R&D database (Pharmaprojects, Informa Group plc) and a bibliographic database of published biomedical literature (Medline, US National Library of Medicine). The date of IND Application to the FDA was taken as the start of clinical development; where this was not available, we used the date that the first clinical trials were undertaken (taken from the published literature) or the date that the first report of clinical trials (typically phase I) was published instead. The dates of MAA and MA were obtained from the EMA website or direct from the MHRA.

The duration of clinical development, as well as the clinical trial and regulatory approval periods, were calculated to the nearest month. Simple descriptive statistics were used to summarise these data and explore differences in durations according to the drug indication (viral disease) and year of licence (1981-1992, 1993-2003 and 2004-2014). The statistical significance of differences in mean duration were determined using unpaired t-tests. Scatter plots were used to visualise trends in development timeframes by year of UK drug launch, and where relevant, Pearson's correlation coefficient and least-squares linear regression lines were calculated. Statistical analyses were conducted using SPSS (v21.0, IBM).

## Results

There were 48 new drugs licensed for the treatment of viral diseases in the UK during the 34 year period from 1981 to 2014, representing a mean 1.4 new drugs per year (Table 1). Almost half of these drugs were licensed in the middle period (1993-2003, 48%), while just 15% were licensed in the earlier period (1981-1992). Over half of new drugs (54%) were initially indicated for HIV infection. The next most frequent initial indication was hepatitis C infection (15%), followed by infection with cytomegalovirus (13%), hepatitis B (8%), herpes simplex virus (4%), influenza virus (4%), and respiratory syncytial virus (2%, full details provided in supplementary file 1).

The overall mean duration of clinical development was 77.2 months, the majority of which was spent in clinical trials before the date of regulatory submission (84%, Table 1). The total time in clinical development increased during the study period, from 58.0 months for drugs licensed 1981-1992, to 91.7 for drugs licensed 2004-2014, a result that was statistically significant (p=0.048). This increase was accounted for by an increase in time spent in clinical trials before regulatory submission, which increased from 41.7 months for drugs licensed 1981-1992 to 78.4 months for drugs licensed 2001-2014 (p=0.027). No equivalent increase in time spend in the regulatory approval period was observed. A statistically significant upward linear trend in the total duration of clinical development (r=0.31, y=1.26 x year – 2442.01, p=0.034, Figure 1) and the clinical trials period (r=0.34, y=1.38 x year – 2695.37, p=0.018) was observed for drugs licensed across the whole study period, suggesting that mean total clinical development and clinical trial durations increased by twelve months every 9.5 and 8.7 year period, respectively. In contrast, no significant linear trend was observed for the duration of the regulatory approval period (r=0.16, y= –0.12 x year + 253.36, p=0.32).

Considering the initial indications for new drugs, those licensed to treat hepatitis C infection had a longer duration of clinical development than those indicated for HIV infection or other viral infections (Table 1), though this result was not statistically significant. A statistically significant

upward linear trend was observed for total clinical development durations for drugs first licensed to treat HIV across the study period (r=0.54, y=1.84 x year – 3606.44, Figure 2). The clinical development durations of drugs initially licensed to treat other viral infections increased at a slower rate, and the trend was not statistically significant (r=0.29, y=0.98 x year –1882.40).

## Discussion

We have shown that for drugs licensed in the UK to treat viral infections, the time spent in clinical development has increased markedly over the last three decades. This increase is due to increasing time spent in clinical trials before regulatory submission; no trend was observed in the time taken for regulatory approval. In addition, drugs licensed for hepatitis C appeared to spend longer in development than those for other viral infections but clinical development durations increased more rapidly for drugs licensed to treat HIV than those licensed to treat other viral infections. Our estimate of the rate of increase in mean time spent in clinical trials prior to regulatory submission is much greater than that found by Kaitin and DiMasi for all drugs approved in the USA between 1980 and 2009 (from 5.7 years in the period 1980-1989, to 6.4 years in the period 2000-2009).[16] However, a more appropriate comparison might be between our results and those for anti-HIV drugs and other anti-infectives, where Kaitin and DiMasi reported a 117% and 57% increase, respectively, in the mean time spend in clinical trials between the periods 1980-89 and 2000-09. Our estimates of the mean time that anti-viral drugs spent in clinical trials prior to filing increased 87% between the periods 1981-92 and 2001-14, and our estimated mean time spent in clinical trials for the period 2004-14 (6.5 years for all anti-viral drugs and 5.3 years for anti-HIV drugs) were similar to those reported by Kaitin and DiMasi for the period 2000-09 (5.0 years for anti-HIV drugs and 6.6 years for other anti-infectives), showing a considerable degree of concurrence between their findings and our own.

This study relied on data from the BNF, MHRA and EMA, ensuring that the identification of drugs was comprehensive and the data on regulatory dates were accurate. For initiation of clinical trials, we relied on the date of IND application, a process which only applies to the USA and not to Europe. This point in the development of a new molecule occurs when the developer "wants to test its diagnostic or therapeutic potential in humans".[14] On a global basis, the IND application may be regarded as a reasonable proxy for the decision to advance development of a new drug beyond pre-clinical testing given that in recent decades the majority of new drugs have been launched in the USA at an earlier or similar time to Europe.[18] The European Union (EU) equivalent process, requiring submission of a request for authorisation of clinical trials, stems from a 2001 Directive[19] and is therefore a more recent development that could not be applied to the study period of interest. We could not determine a date for IND application in six cases (representing drugs launched between 1982 and 1996). The association between clinical development time and year of launch was maintained after excluding these drugs from the analysis (r=0.42, y=1.99 x year – 3912.46, p=0.006).

Our study addresses only the clinical development period of drug development; it omits the time and resources needed to discover and bring a candidate molecule through laboratory and initial animal studies, and does not consider activities post-approval, including marketing, phase IV studies, evidence reviews and the generation of guidance to clinicians and health services.[6 11 20] Several commentators have described models of the translation pathway providing consistent definitions for different stages of the process and allowing comparison between studies and evaluation of efforts to reduce unwarranted delays. Trochim *et al*[11] proposed a "process marker" model that recognises translational research as a continuous process that may be "bidirectional, variable, [and] complex" with observable milestones along a generalised pathway allowing measurement of time elapsed between them. Recognising that the process marker model may be more appropriate to technology driven developments, Hanney *et al* have proposed a generalisable model for all healthcare innovation, suggesting a matrix of four different "tracks" in the innovation process, building from

discovery research, through human research and research review, to clinical and health service/public policy development, and finally clinical practice.[20] This recognises the overlapping nature of research translation activities, and allows for the initiation of different tracks at different times despite relevant research still occurring in 'earlier' tracks. Our study considers the 'Clinical Trials System' element of the translational research continuum described by Trochim et al[11] and overlapping elements of tracks 2 and 3 in Hanney et al's description of the innovation process.[20] Taken together, these help identify drivers of the trends seen. In this way, the increasing demands of regulators that have led to increasing complexity of clinical trial programmes are highly relevant to the increase in clinical trial periods we have observed. This has been recognised by policy-makers, who have agreed revisions to the 2001 EU Clinical Trials Directive (effective from 2004), widely seen as having a negative impact on translational research, increasing administrative burdens and waiting periods,[21-24] and introduced a range of initiatives in the USA and Europe to provide a more rapid pathway to approval for innovative drugs that address serious conditions, urgent public health needs, or specific patient groups.[25 26]

Despite the introduction of these initiatives, visual inspection of our data (Figures 1 and 2) shows no apparent step change consistent with a sudden change in the regulatory environment (such as the creation of the EMA or implementation of the EU Clinical Trials Directive). This may be expected given the long lead times for planning and conducting clinical trial programmes, though further analysis shows no association between the duration of clinical development and the year when clinical development commenced (r=0.04, y= −0.16 + 399.67, p=0.80). However, the impact of regulators can be seen in the shorter development durations seen for HIV drugs, which have previously been reported as receiving Marketing Authorisation without "large-scale human clinical trials",[27] though our data suggest this difference is now lessening. This is an example of regulators responding to a public health need and being willing to adopt a different view of the risk-benefit in specific circumstances.[20] One current regulatory development applicable to the UK is the MHRA's

Early Access to Medicines Scheme, which allows patients with serious conditions to access medicines that have not yet been approved where there is a clear unmet medical need.[28] This will not necessarily reduce time to Marketing Authorisation, but may facilitate collection of real-world data to support earlier adoption of innovative new drugs. In this way it has parallels with the EMA's adaptive licensing pilot, but this EU-wide initiative also has the potential to bring forward the date of a drugs initial Marketing Authorisation, allowing first approval in highly selected patient populations based on more limited initial clinical studies.[29] Both these examples are indicative of a wider move towards early dialogue between regulators and commercial developers,[26] a move mirrored by health technology assessment (HTA) agencies in Europe, either alone or in parallel with regulators.[26 30] Early dialogue may or may not lead to a reduction in clinical development durations, but it is likely to be reflected in the design and conduct of late-phase clinical trial programmes.[30 31] This will have an uncertain effect on clinical trial times if HTA agencies demand longer-term patient-related outcomes rather than proxy measures on which to judge value, but it may be expected to speed up the total time to adoption and diffusion of those drugs judged to be most clinically and cost-effective.

The past few decades have seen the introduction of many novel anti-viral drugs, but the time spent in clinical development before drug approval has increased substantially. We found no evidence that this trend in increasing clinical development timescales is levelling off, though many of the current initiatives aimed to speed access to innovative new medicines are too recent to have affected clinical trial programmes for drugs launched up to 2014, and will therefore require further evaluation in the coming years. However, it is important to stress that adequate time spent in clinical trials is critical to generate evidence of safety, efficacy and cost-effectiveness,[20] and that regulators require adequate time to consider this evidence and strike an appropriate balance between benefit and risk.[32] There are necessarily limits to clinical development durations, but this is only one part of the whole discovery to clinical practice translational pathway, and increased time in one part of the pathway may be offset by gains elsewhere. Further research should incorporate measures of pre-

clinical and adoption timeframes in order to gain a complete picture and ensure there are no

unwarranted delays in novel drugs reaching patients in need.

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**Figure 1. Duration of clinical development for anti-viral drugs by year of first licence in the UK, 1981-2014.**



$$y = 1.26 \times year - 2442.01$$
$$p = 0.034, r = 0.31$$

Months

Year of first UK licence

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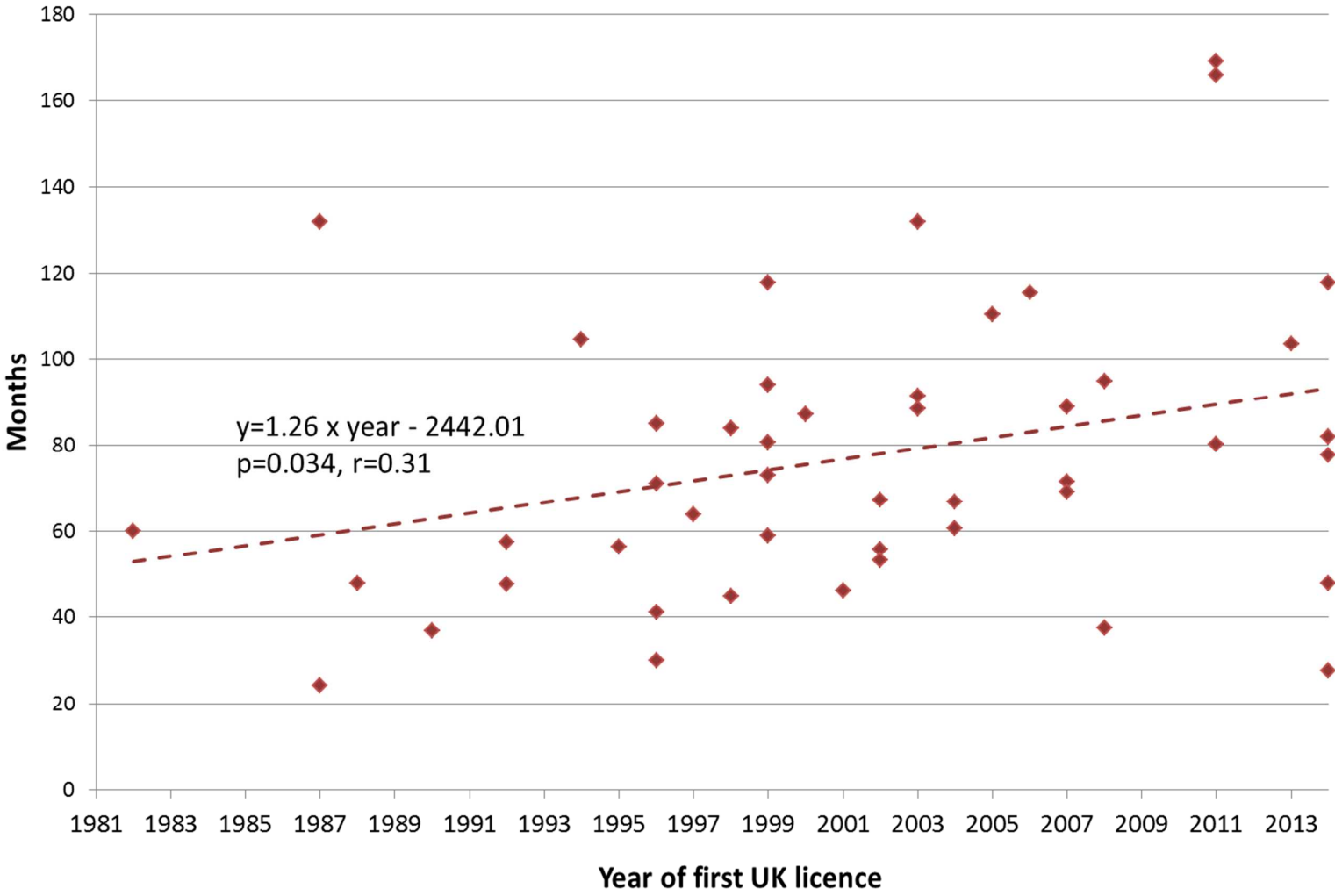41
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**Figure 2. Duration of clinical development for anti-viral drugs indicated for HIV and other viral infections by year of first licence in the UK, 1981-2014.**
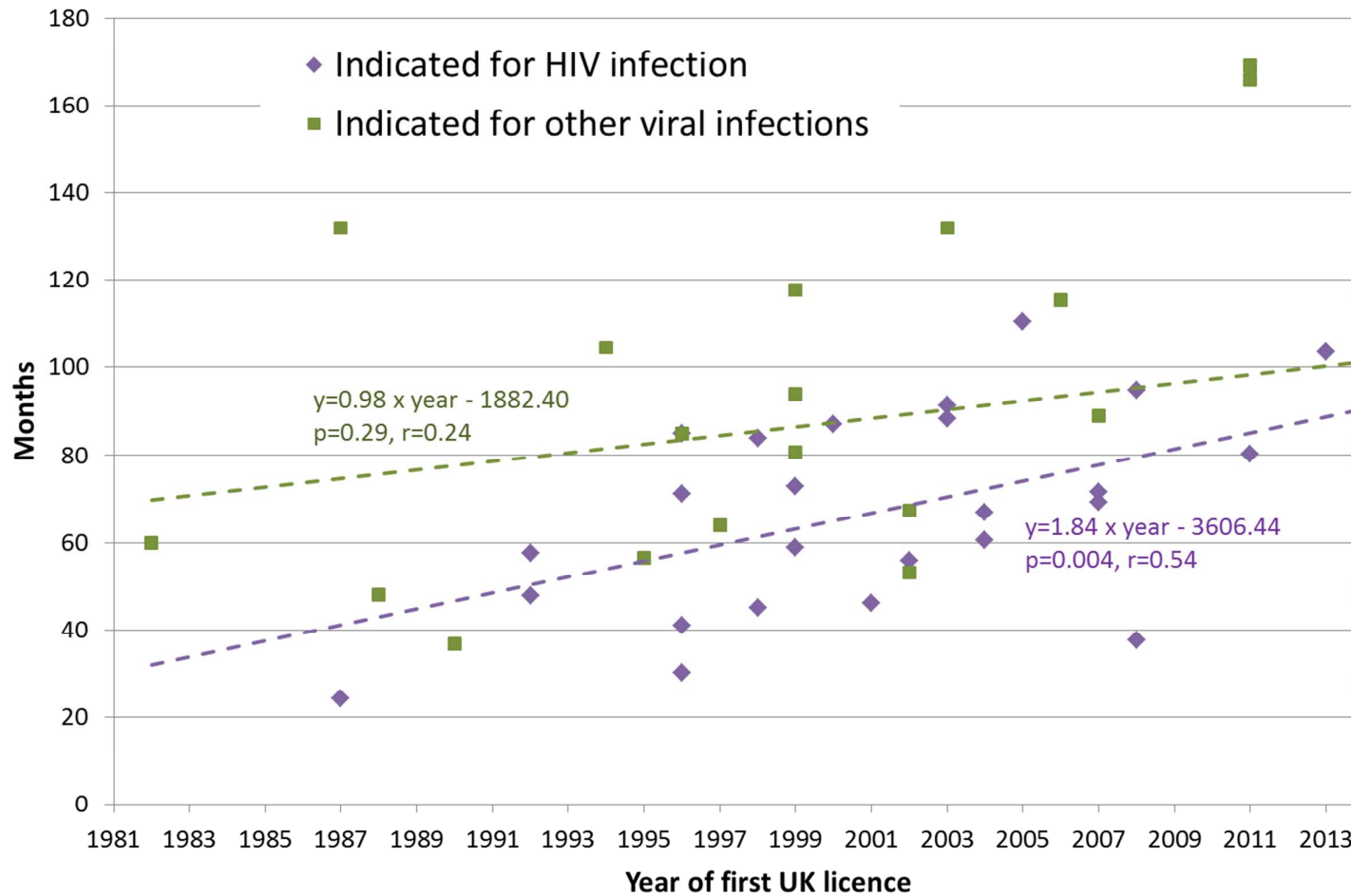
**Table 1. Duration of clinical development for anti-viral drugs, in total and sub-divided into clinical trials and regulatory approval periods, by year of first licence and indication in the UK, 1981-2014.**

| | Number | Duration of development (months) | | | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | Clinical trials period | | | | Regulatory approval period | | | | Total duration | | | | | |
| | | Mean | SE | 95% CI | | Mean | SE | 95% CI | | Mean | SE | 95% CI | | | |
| All new drugs | 48 | 64.6 | 4.70 | 55.9 to | 73.3 | 12.6 | 0.96 | 10.8 to | 14.7 | 77.2 | 4.75 | 68.7 to | 86.6 | | |
| Drugs licensed between | | | | | | | | | | | | | | | |
| 1981-1992 | 7 | 41.7 | 9.90 | 23.5 to | 62.6 | 16.3 | 5.02 | 7.3 to | 26.8 | 58.0 | 13.2 | 37.6 to | 86.4 | | |
| 1993-2003 | 23 | 63.2 | 5.34 | 53.6 to | 73.7 | 11.2 | 1.01 | 9.3 to | 13.1 | 74.4 | 5.21 | 64.9 to | 84.9 | | |
| 2004-2014 | 17 | 78.4 | 9.02 | 61.5 to | 96.7 | 13.3 | 1.10 | 11.3 to | 15.6 | 91.7 | 8.80 | 75.2 to | 108.9 | | |
| Initial licensed indication | | | | | | | | | | | | | | | |
| HIV infection | 26 | 55.8 | 4.18 | 47.5 to | 64.1 | 11.8 | 0.94 | 10.0 to | 13.5 | 67.6 | 4.43 | 58.7 to | 76.5 | | |
| Hepatitis C infection | 7 | 92.1 | 20.52 | 52.8 to | 133.4 | 13.9 | 4.69 | 8.4 to | 25.2 | 106.0 | 21.00 | 63.7 to | 147.2 | | |
| Other viral infection | 15 | 66.8 | 7.97 | 51.2 to | 83.3 | 13.5 | 1.59 | 10.3 to | 16.4 | 80.3 | 7.32 | 66.6 to | 95.3 | | |

## Contribution of the authors

DJW and AJS conceived the original study idea, and EH and LL-P contributed to the development of the study design and methods. EH collected the data and carried out the analysis with assistance from LL-P and DJW. All authors (DJW, EH, LL-P and AJS) were involved in the interpretation of the results. DJW produced the initial draft of the paper, which was then circulated repeatedly to all authors for critical revision. DJW, EH, LL-P and AJS read and approved the final version. All authors had full access to all of the study data (including statistical reports and tables), and can take responsibility for the integrity of the data and the accuracy of the analysis. DJW is the guarantor.

## Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors have financial support from the National Institute for Health Research (NIHR) for the submitted work; all authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and all authors have no other relationships or activities that could appear to have influenced the submitted work.

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## Data sharing statement

The dataset used for analyses has been provided as a supplementary file, and has been added to the

Dryad repository (doi:10.5061/dryad.nh5nr), which will provide a permanent, citable and open

access home for the dataset. No additional unpublished data are available.

## References

1. Satcher D. Emerging Infections: Getting Ahead of the Curve. Emerging Infectious Disease. March 1995; 1(1).

2. Marston HD, Folkers GK, Morens DM, et al. Emerging Viral Diseases: Confronting Threats with New Technologies. Science Translational Medicine 2014;**6**(253):ps10.

3. Hogg R, Lima V, Sterne JA, et al. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;**372**(9635):293-9.

4. Sheridan C. FDA approvals usher in the post-interferon era in HCV. Nature Biotechnology 2014;**32**(1):3-5.

5. House of Commons Select Committee on Health. The Influence of the Pharmaceutical Industry. London: House of Commons, 2005.

6. Mestre-Ferrandiz J, Sussex J, Towse A. The R&D cost of a new medicine. London: Office of Health Economics, 2012.

7. Scannell JW, Blanckley A, Boldon H, et al. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 2012;**11**(3):191-200.

8. Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov 2011;**10**(6):428-38.

9. Hay M, Thomas DW, Craighead JL, et al. Clinical development success rates for investigational drugs. Nature Biotechnology 2014;**32**(1):40-51.

10. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. Journal of the Royal Society of Medicine 2011;**104**:510-20.

11. Trochim W, Kane C, Graham MJ, et al. Evaluating Translational Research: A Process Marker Model. Clinical and Translational Science 2011;**4**(3):153-62.

12. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 2010;**9**(3):203-14.

13. Keyhani S, Diener-West M, Powe N. Are development times for pharmaceuticals increasing or decreasing? Health Affairs 2006;**25**(2):461-68.

14. US Food and Drug Administration. Investigational New Drug (IND) Application. Last update 27/10/2015. http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm. Accessed 16/06/2015.

15. US Food and Drug Administration. New Drug Application (NDA). Last update 02/03/2015. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm. Accessed 16/06/2015.

16. Kaitin KI, DiMasi JA. Pharmaceutical Innovation in the 21st Century: New Drug Approvals in the First Decade, 2000-2009. Clinical Pharmacology & Therapeutics 2011;**89**(2):183-88.

17. Pregelj L, Verreynne M, Hine D. Changes in clinical trial length. Nat Rev Drug Discov 2015;**14**(5):307-08.

18. Downing NS, Aminawung JA, Shah ND, et al. Regulatory Review of Novel Therapeutics — Comparison of Three Regulatory Agencies. New England Journal of Medicine 2012;**366**(24):2284-93.

19. European Commission. Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1). 2010. C82/01. http://ec.europa.eu/health/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf.

20. Hanney SR, Castle-Clarke S, Grant J, et al. How long does biomedical research take? Studying the time taken between biomedical and health research and its translation into products, policy, and practice. Health Research Policy and Systems 2015;**13**(1):1.

21. Frewer LJ, Coles D, Champion K, et al. Has the European Clinical Trials Directive been a success? BMJ 2010;**340**:c1862.

22. Gulland A. Number of global clinical trials done in UK fell by two thirds after EU directive. BMJ 2009;**338**:b1052.

23. Hartmann M. Impact assessment of the European Clinical Trials Directive: a longitudinal, prospective, observational study analyzing patterns and trends in clinical drug trial applications submitted since 2001 to regulatory agencies in six EU countries. Trials 2012;**13**:53.

24. Watson R. EU nations approve law to overhaul clinical trials. BMJ 2013;**347**:f7682.

25. Baird LG, Banken R, Eichler HG, et al. Accelerated Access to Innovative Medicines for Patients in Need. Clinical Pharmacology & Therapeutics 2014;**96**(5):559-71.

26. Grainger D. Is this the real life? Is this just fantasy? International Journal of Technology Assessment in Health Care 2014;**30**(03):239-40.

27. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really $802 million? Health Affairs 2006;**25**(2):420-28.

28. Medicines and Healthcare Products Regulatory Agency. Apply for the early access to medicines scheme (EAMS). https://www.gov.uk/apply-for-the-early-access-to-medicines-scheme-eams#overview. Accessed 16/06/2015.

29. Eichler HG, Baird LG, Barker R, et al. From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients. Clinical Pharmacology & Therapeutics 2015;**97**(3):234-46.

30. Jönsson B. Bringing in health technology assessment and cost-effectiveness considerations at an early stage of drug development. Molecular Oncology 2015;**9**(5):1025-33.

31. Mestre-Ferrandiz J, Deverka P, Pistollato M, et al. The current drug development paradigm: responding to US and European demands for evidence of comparative effectiveness and relative effectiveness. Occasional Paper. London: Office for Health Economics, 2014.

32. Tominaga T, Asahina Y, Uyama Y, et al. Regulatory Science as a Bridge Between Science and

Society. Clinical Pharmacology & Therapeutics 2011;**90**(1):29-31.

**Supplementary data file:**

**Anti-viral drugs licenced for use in the UK, 1981-2014 with key development dates and initial licensed indication.**

| Drug name | Investigational New Drug (IND) Application (or first report of clinical trial where IND not known) | Date of Marketing Authorisation Application to EMA or MHRA | Date Marketing Authorisation granted for the UK | Initial licensed indication (viral infection) |
|---|---|---|---|---|
| Abacavir | Jun-93 | Jun-98 | Jul-99 | Human Immunodeficiency Virus |
| Aciclovir | (1977) | Jun-81 | Jun-82 | Herpes Simplex Virus |
| Adefovir dipivoxil | Mar-92 | Mar-02 | Mar-03 | Hepatitis B |
| Amprenavir | Jul-93 | Oct-98 | Oct-00 | Human Immunodeficiency Virus |
| Atazanavir | Aug-98 | Apr-02 | Mar-04 | Human Immunodeficiency Virus |
| Boceprevir | Sep-97 | Nov-10 | Jul-11 | Hepatitis C |
| Cidofovir | Mar-92 | Dec-95 | Jul-97 | Cytomegalovirus |
| Daclatasvir | Oct-07 | Dec-13 | Aug-14 | Hepatitis C |
| Darunavir | Mar-01 | Jan-06 | Feb-07 | Human Immunodeficiency Virus |
| Didanosine | Jun-88 | Jun-91 | Jun-92 | Human Immunodeficiency Virus |
| Dolutegravir | Jul-07 | Dec-12 | Jan-14 | Human Immunodeficiency Virus |
| Efavirenz | Jun-94 | Jun-98 | May-99 | Human Immunodeficiency Virus |
| Elvitegravir | Mar-05 | May-12 | Nov-13 | Human Immunodeficiency Virus |
| Emtricitabine | Jun-96 | Dec-02 | Oct-03 | Human Immunodeficiency Virus |
| Enfuvirtide | Oct-95 | Sep-02 | May-03 | Human Immunodeficiency Virus |
| Entecavir | Nov-96 | Sep-04 | Jun-06 | Hepatitis B |
| Etravirine | Oct-00 | Jul-07 | Aug-08 | Human Immunodeficiency Virus |
| Famciclovir | (1985) | Nov-93 | Feb-94 | Herpes Simplex Virus |
| Fomivirsen | Nov-92 | May-98 | Aug-99 | Cytomegalovirus |
| Fosamprenavir | Jun-99 | Dec-02 | Jul-04 | Human Immunodeficiency Virus |
| Foscarnet sodium | Jan-87 | Dec-87 | Feb-90 | Cytomegalovirus |

| Ganciclovir | (1984) | Jun-87 | Jun-88 | Cytomegalovirus |
|---|---|---|---|---|
| Indinavir sulphate | Jul-93 | Mar-96 | Dec-96 | Human Immunodeficiency Virus |
| Lamivudine | Aug-89 | Jun-95 | Sep-96 | Hepatitis B |
| Ledipasvir | Jul-12 | Feb-14 | Nov-14 | Hepatitis C |
| Lopinavir | May-97 | Jun-00 | Mar-01 | Human Immunodeficiency Virus |
| Maraviroc | Dec-01 | Dec-06 | Sep-07 | Human Immunodeficiency Virus |
| Nelfinavir | Jun-94 | Feb-97 | Mar-98 | Human Immunodeficiency Virus |
| Nevirapine | Apr-91 | Jun-97 | Apr-98 | Human Immunodeficiency Virus |
| Oseltamivir | Nov-96 | Feb-01 | Jun-02 | Influenza |
| Palivizumab | Oct-91 | Jul-98 | Aug-99 | Respiratory Syncytial Virus |
| Raltegravir | Nov-04 | Apr-07 | Jan-08 | Human Immunodeficiency Virus |
| Ribavirin | (1976) | Dec-83 | Jun-87 | Hepatitis C |
| Rilpivirine | Mar-05 | Sep-10 | Nov-11 | Human Immunodeficiency Virus |
| Ritonavir | May-94 | Feb-96 | Nov-96 | Human Immunodeficiency Virus |
| Saquinavir | Mar-90 | Sep-95 | Feb-96 | Human Immunodeficiency Virus |
| Simeprevir | Jul-04 | Apr-13 | May-14 | Hepatitis C |
| Sofosbuvir | Jan-10 | Apr-13 | Jan-14 | Hepatitis C |
| Stavudine | (Jun-89) | Jul-95 | Jul-96 | Human Immunodeficiency Virus |
| Telaprevir | Aug-97 | Dec-10 | Sep-11 | Hepatitis C |
| Telbivudine | Dec-99 | Feb-06 | Apr-07 | Hepatitis B |
| Tenofovir disoproxil fumarate | Jun-97 | May-01 | Feb-02 | Human Immunodeficiency Virus |
| Tipranavir | Aug-96 | Nov-04 | Oct-05 | Human Immunodeficiency Virus |
| Valaciclovir | Mar-91 | Aug-94 | Nov-95 | Cytomegalovirus |
| Valganciclovir | Oct-97 | Nov-01 | Mar-02 | Cytomegalovirus |
| Zalcitabine | (Sep-89) | Feb-92 | Jun-92 | Human Immunodeficiency Virus |
| Zanamivir | Aug-89 | Jan-99 | Jun-99 | Influenza |
| Zidovudine | Jul-85 | Jan-87 | Jul-87 | Human Immunodeficiency Virus |