PPDD2020 Deliverables & Cases

Grading

Grades will be determined as follows:
Class participation – 20%
In the news presentation – 20%
One-page summary – 20%
Oral presentation – 20%
Written proposal – 20%

Class participation

The interactive component of this course is established through insightful questions and critical thinking of students taking the course. It is therefore crucial that you prepare for class and are ready to ask insightful questions on the topic of each session. Students are required to have their **cameras on** throughout the sessions and use their **first and last names as their identifier** in Zoom. Questions are encouraged at all times during the session but are essential in the Q&A part of each class. To facilitate an active participation, **each team will be assigned to moderate the discussion of one or two sessions**.

Moderating a discussion section includes selecting who can ask a question first if multiple audience members have questions to ask. It also includes preparing 3-5 questions for the speaker. In case there are no initial questions from the rest of the class, moderators can begin with: "as people are gathering their thoughts, I was wondering [insert prepared question here]".

In case you miss a class, we ask you to watch the recording of the class, write a short summary and think of one question for the instructor(s) of the missed question. This question should not have been addressed in the Q&A of the lecture. The summary and question should be received by the TAs (Deborah_Plana@hms.harvard.edu & aboghozi@mit.edu) before the beginning of the next class.

Key Dates & Descriptions

September 9th 3pm: Case Study Topic Selection (report choice here)
Variable – News of the week (15 minutes, group) Slides due at 3pm on the day of presentation
November 2th – One-page summary of policy proposal & annotated bibliography (group)
December 3th—Written proposal (5-10 pages, group)
December 9th – Oral presentation (20 minutes, group) slides due at 3pm December 9th

In the news presentation

15 minutes, including Q&A
As a group, you will pick a drug development related issue that is currently (or was recently) in the news. You will present the issue to the class and explain how it relates to drug development and why it is relevant to the class. It is important to highlight the diversity of interests that different stakeholders have in the issue you present. We ask that you share your slides with us.

Slides should be received by the TAs (Deborah_Plana@hms.harvard.edu & aboghozi@mit.edu) before the beginning of class.

One-page summary

As is common for applications to fellowships and grants, we ask that you deliver a one-page summary of your proposal along with an annotated bibliography of the papers you have used or will use for the full proposal (each annotation is 2-3 phrases). The summary should be fully referenced. We expect the format to be compliant with NIH guidelines (see here). Citations should be compliant with academic standards (see here and here).

Oral presentation

20 minutes, including Q&A. Your group will present a debate chosen from the topics below. It is important to highlight the diversity of interests that the different stakeholders have in the issue you are tackling.

Full proposal

The full proposal is an in-depth (5-10 pages) discussion of your proposal. Just like the presentation, we expect you to understand what each of the stakeholders' interests are. The ideal policy would satisfy all of these interests, but this is rarely practically possible. In your full proposal, we expect you to explain: i) who's interests you prioritized and why, ii) what the risks are of not meeting everybody's interest in your particular case, and iii) how your plan is robust with respect to these identified risks. We expect format to be compliant with NIH guidelines (see here). Citations should be compliant with academic standards (see here and here).

Your work will be evaluated on:

- Clarity of presentation (text, slides & voice-over)
- Knowledge of the subject
- Identification of stakeholders involved
- Reasonability and feasibility of the proposed solution(s)

Case titles

Treating opioid use disorder (OUD)

Case 1: Should physicians be allowed to opt-out of prescribing medications for OUD and instead refer those patients to a different provider?

Case 2: Should the current waiver system be modified for prescribing buprenorphine? If so, how?

Case 3: Is it necessary and possible to develop a new OUD drug without the potential for misuse?

Drug Pricing - Biologics

Case 4: Should the US adopt the EU pricing models for biosimilars? Is there another model that would reduce the price of biologics?

Case 5: Should the characteristics of a disease (such as incidence, severity, and affected patient populations) impact regulatory pricing considerations for its associated therapeutics?

Rare diseases

Case 6: For which diseases and by which mechanism should the government prioritize funding for academic research and industry drug development?

Case 7: Do previous outcomes of government funding of academic rare disease research warrant further funding in this area?

Case 8: Does the current system for funding start-ups do enough to promote entrepreneurial innovation in rare disease drug development?

Antimicrobial stewardship

Case 9: How should the costs and benefits of an antimicrobial stewardship for hospitals be weighed against their impact on the general public?

Case 10: How should a physician prioritize the tradeoffs between antibiotic prescription and non-use for the individual patient compared to the effects on the rise of antimicrobial resistance?

COVID-19 publication mistakes and retractions

Case 11: How should the time and resources required for changes to improve the peer-review process be weighed against the urgent need for results about new treatments in the face of an emergency?

Case Prompts

Treating opioid use disorder (OUD)

The opioid epidemic is one of the deadliest epidemics in recent history – claiming an estimated 200,000 lives[1]. The current gold standard for opioid use disorder (OUD) treatment is counseling assisted by medication. Two pharmacological interventions exist for OUD: methadone and buprenorphine. The former is distributed in a limited number of opioid treatment programs, mostly in large urban centers, and requires patients to report on-site in order to receive treatment. The later, marketed as Suboxone, was approved in 2002 by the FDA, and can be dispensed by physicians in the outpatient setting, increasing treatment access as compared to methadone[2]. However, physicians interested in prescribing buprenorphine must qualify for a waiver from the Drug Enforcement Administration. This process requires eight hours of training and successful completion of an application to the Substance Abuse and Mental Health Services Administration. After receiving a waiver, physicians can only prescribe buprenorphine to 30 patients for the first year, and then must submit a second application if they wish to increase that number to 100[3].

Critics of the waiver system argue that it limits the ability to treat patients with OUD, and that it is unethical for individual physicians to choose to abstain from prescribing buprenorphine. Supporters of the system point out that buprenorphine is a drug with a high misuse potential, and that amid the opioid epidemic, regulatory agencies should be taking more rather than fewer steps to limit access to opioids[4]. Meanwhile, research efforts are underway to find alternative ways to diagnose and treat OUD, including finding novel non-opioid medical alternatives[5].

In your consideration of the case prompt, you may find it useful to consider the following questions:

1. *Describe the biological mechanisms of methadone and buprenorphine. Why are they used in treating OUD, and why do they carry with them the risk for misuse?*
2. *Summarize the evidence for buprenorphine and methadone's effects in treating OUD. How well do they work, and for which patients?*
3. *What alternative options have been suggested for the current buprenorphine waiver system?*

4. *How do socioeconomic status, race, and ethnicity affect physicians' prescribing rates of OUD medications?*

Drug Pricing- Biologics

Biological medical products, also known as biologics, made up 2 percent of drug prescriptions, but 37 percent of net drug spending in the United States in 2017[6]. Biologics include therapeutic proteins such as insulin, monoclonal antibodies such as nivolumab, and vaccines such as those for influenza[7]. As compared to traditional small molecule drugs, such as statins for elevated cholesterol levels, biologics are manufactured in living cells, which makes them more complex and more expensive to produce. Additionally, developing "generic equivalents" of biologics, known as biosimilars, is costlier and more time consuming than developing small molecule generics. This difference is partly due to legal and regulatory considerations in the United States[8]. As of May 2018, 9 biosimilars had been approved by the FDA in the U.S.; in contrast, 40 such approvals have taken place in Europe[9]. Additionally, the high cost of sofosbuvir to treat Hepatitis C[10], insulin to treat diabetes[11], and epinephrine auto-injectors for asthma and allergic reactions[12], have ignited a debate to change the regulation of biosimilars in the U.S.

In your consideration of the case prompt, you may find it useful to consider the following questions:

1. *What are the technical differences between producing small molecules and biosimilars that contribute to the high production cost of the latter?*
2. *Are high prices the incentive needed to promote drug development in certain disease areas?*
3. *Are there other policy levers available that may provide similar incentives for drug companies but at a lower direct cost to consumers?*
4. *Sofosbuvir is available for $4 in India, as compared to $1000 in the United States. How would global drug innovation and pricing be impacted by changes in how the US pays for drugs?*

Rare diseases

More than 90% of rare diseases (defined as conditions that affect less than 200,000 people) still lack an effective treatment, which in aggregate affect about 30 million people in the United States. The paucity of treatments for patients with rare diseases is considered one of the greatest contemporary health disparities in our medical system[13]. Little basic science research exists for many of these diseases, making it difficult to identify potential candidates for drug development[13]. Even after a target of interest has been identified, drug development in this setting is challenging due to the high cost of drug manufacturing, along with the low likelihood for a return-on-investment given the small market size after drug approval[13]. Additionally, clinical trials in this space have a small number of patients that is eligible for enrollment, making it difficult to reach the statistical power necessary to consider an intervention efficacious[13].

The relative cost and effectiveness of public and private efforts in rare disease pharmaceutical development has been widely debated[14]. Regulatory activities to increase approval rates for rare disease drugs include the US Orphan Drug Act of 1983[15]; academic projects include the Broad Institute's Rare Genomes Project[16]; and over 100 companies are currently developing treatments for rare diseases[17].

In your consideration of the case prompt, you may find it useful to consider the following questions:

1. *Summarize the impact of recent regulatory and academic efforts to increase rare diseases research.*
2. *What is the role of patient-advocates in rare diseases drug development?*
3. *Discuss successful and failed attempts by start-ups to address unmet needs in rare diseases.*

Antimicrobial Stewardship

The problem of antimicrobial resistance involves stakeholders and complex incentives at all levels of the health system (WHO Fact Sheet, 2018)[18]. Individual providers have an immediate incentive to prescribe antibiotics, without consideration to the broader problem of antimicrobial resistance. Hospitals also must ensure prescription of antibiotics in appropriate cases while managing costs[19]. On the societal level, incentives to develop and market new antibiotics are affected by market failures[20].

The Society for Healthcare Epidemiology of America and Infectious Diseases Society of America jointly recommend that hospitals "establish a system for monitoring bacterial resistance and antibiotic usage," "establish practice guidelines and other institutional policies," and measure outcomes to evaluate policy effectiveness, among other practices[21]. Hospital-level antimicrobial stewardship initiatives include a range of initiatives including education, guidelines, prescription restrictions, review and feedback, computer assistance (decision-support), and antimicrobial cycling[22].

Digital tools therefore provide an opportunity for both individual providers and hospital administration to evaluate and adapt their practice [19, 23]. Electronic medical records (EMR) tools provide both the data necessary to understand practice at the site and an opportunity for clinical decision support at the point of care. They therefore provide the opportunity to evaluate practice at the site to develop and adapt guidelines, and a means to communicate updated guidelines in a usable format.

A number of cases have demonstrated successful hospital-level enactment of antimicrobial stewardship initiatives and suggested best practices for the approach [24–27]. However, the potential for ancillary costs, provider dissatisfaction and resulting implementation challenges is great. EMR support for antimicrobial stewardship and associated analytical capacity at the site may be costly [28], or providers may cite satisfactory reasons for their prescribing tendencies on the individual level[29].

In your consideration of the case prompt, you may find it useful to consider the following questions:

1. *What roles should various stakeholders play in program design, including hospital administrators, attending physicians, residents, nurses, and pharmacists?*
2. *How would you use EMR to inform the policy? What types of data would you need? What baseline would be acceptable, how would you interpret outcomes? How might providers respond (in terms of both provider satisfaction and data integrity)?*

COVID-19 publication mistakes and retractions

SARS-COV-2 is a novel respiratory virus, which had its first confirmed case in the United States in January 2020[30]. No treatment options or vaccines were approved for the disease. As a result of the virus' unprecedented public health impact, the U.S. Secretary of Health and Human Services declared a state of emergency on January 31, 2020[31]. As a consequence of this declaration, the U.S. Food and Drug Administration was able to issue a series of Emergency Use Authorizations (EUAs) for the use of potentially promising treatment options for COVID-19 in the absence of formal FDA approval, including for drugs such as hydroxychloroquine and remdesivir, as well as convalescent plasma[32]. The decision to grant or retract EUAs is partly based on published evidence from clinical trials.

The accuracy of the reports from many preprint and peer-reviewed clinical studies came under scrutiny during the pandemic. For instance, a publication on the effectiveness hydroxychloroquine from the high-profile medical journal *The Lancet,* was retracted due to concerns raised about whether the data used to generate the results in the study was falsified[33]. Such controversies are especially concerning because incorrect reporting of clinical

trial results could alter FDA drug approval and clinical practice, in addition to eroding public trust in science. As a result, many have called for reforms to the peer-review process to ensure the integrity of reported data and its analysis[34]. Others have argued that such mistakes stem from issues in the academic incentive structures around publishing as well as the urgent need for data on treatment efficacy during this unique emergency[35].

In your consideration of the case prompt, you may find it useful to consider the following questions:

1- *What reforms to the peer-review system could decrease the likelihood of publishing falsified or incorrect clinical trial results?*
2- *How should the normal clinical trial publication process be modified in the face of an emergency?*
3- *What is the role of academic institutions, journal editors and reviews, and regulatory agencies in confirming the legitimacy of new data and reported results? Which entity should ultimately bear the responsibility of confirming the accuracy of information reported in the clinical literature?*

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