Overview

This edition of the drug times focuses on virtual clinical trials, use of artificial intelligence in drug discovery and the untold story of prazosin. In addition, the drug safety alerts, new drug approvals and new indications for some existing drugs are also highlighted.

Virtual Clinical Trials

What is a Virtual clinical trial (VCT)?

A virtual clinical trial is one where patient assessment and data collection happen in a remote setting and not in traditional settings, such as a health center or hospital. Global Site Solutions Summit survey has identified the three virtual components as technology of mobiles, digital patient diaries and digital devices which can be worn. The synonyms for VCT are “decentralized trials”, “remote trials” and “direct-to-patient trials”.

What are the types of VCT?

In true virtual trial, there are neither physical sites nor face-to-face interactions with patients. Hybrid trials involve patient-facing technology. These trials include direct-to-patient interaction by the Principal investigator (PI) or participating physicians.

When did it start?

The first virtual clinical trial was conducted by Elli Lilly who tested tadalafil on erectile dysfunction and used online questionnaires to fill details during the study. Later, it was by Pfizer who conducted the first total virtual clinical trial where they used smartphones and the web to recruit patients and collect data. They also compared this model with the conventional method of conducting trials. However, they faced a problem because of the limited skill in using technology.
Virtual Clinical Trials

What happens in VCT?
The focus is on trying to deliver patient-centric practices to improve clinical trial participation by reducing the burden on patients. Though it had been happening in a few places, the recent pandemic has turned it into a necessary reality. A virtual clinical trial can be customized to the needs of each patient and trial design.

For example, traditional on-site activities such as dosing, lab work, and follow-up can be conducted remotely at home or through a hybrid model that combines both on-site and at-home visits. In some cases, the investigational product (IP) may be shipped directly to the patient or brought to the patient by a traveling nurse. In other situations, nurses conduct at-home visits to dose patients. They also collect demographic information, vitals, and perform simple lab work. When needed, a patient might visit a local lab for more complex lab work. The investigator/doctor can conduct some visits with the patient through telemedicine as well.

Advantages
- Improves patient recruitment and retention for trials by reducing the patient burden of travel and time going to physical sites
- Finding the right patients by removing geographic barriers to patient eligibility
- Aged, patients with disability, bedridden patients, and patients from rural areas can participate
- Offers a flexible and fully integrated hybrid site model customized to the comfort levels of the patients, sites, sponsors, etc.
- Can be used to study rare diseases since recruitment will be wide.
- Since patients can be recruited from different parts of the world it will be a true representation
- Overcoming COVID-19 restrictions and able to conduct clinical trials irrespective of restrictions
- It may be economical too

Limitations
- There may be no representation of population who are naïve to technology
- Data compilation and analysis from too many technologies and devices may be difficult
- Since there is no direct contact with doctors, adverse effects may go unrecognized. Patients cannot be monitored well
- Patient confidentiality may be a concern
- Regulatory bodies may not accept digital end points
Artificial intelligence (AI) and machine learning has deeply penetrated into our lives. It is not just Alexa of amazon or facial recognition, AI is currently being utilized by the pharmaceutical companies for drug discovery and research. This write up familiarizes the readers with use of AI in drug discovery process.

Artificial Intelligence

It is a concept in which machines simulate human thinking. With the help of AI, machines do not require to be pre-programmed, instead they use their own intelligence to carry out the assigned task. AI functions through various algorithms and deep learning neural networks.

Artificial intelligence in drug discovery

Important applications of AI in drug discovery are as follows:

1. **Prediction** - Traditionally, drug discovery requires researchers to screen a large number of compounds to identify one molecule which could be the potential drug. This involves lot of time and money. It takes around 8 months for drug discovery using AI as against 4 to 5 years using the traditional processes. Moreover, even if a molecule shows promising results in the laboratory, it might fail in the clinical trials. Data suggests that only around 10% drugs make it to phase I clinical trials. AI helps in screening millions of molecules virtually and eventually giving a choice of 3 to 4 molecules to the researcher to synthesize and optimize and ultimately test in clinical trials.

2. **Innovation** – In addition to prediction, AI also helps in inventing molecules where it helps researchers to synthesize new molecules with all desired properties with help of machine learning.

3. **Preclinical studies** – AI can be utilized in PK/PD studies as well as toxicity studies. Machine learning models are used to predict the dose response relationship as well as the toxicities. Use of AI can curtail expensive time consuming toxicity studies.

4. **Clinical trials** - Prediction of outcome of drug treatment in diseases can be effectively done using AI. It will also help in patient recruitment by identifying patients based on their genetic makeup leading to successful trials. It was observed that the medication adherence increased in patients when AI was used during trials. AI also helps in monitoring of adverse drug reactions in all phases of the trials. AI can also be utilized for drug repurposing.

Reference - [www.nature.com/biopharmdeal | June 2021 | B37]
Future Prospects

The most important drawback is the herculean effort required to convert the traditional research into a language that the computer understands. The whole AI system is dependent on high quality data. Security issues linked with such vast data is another important concern. In spite of the current challenges, use of AI will definitely expedite the drug discovery in future and will definitely complement the traditional discovery process by multiple means.

Covid-19 Booster Dose

- As per WHO, booster doses are administered to people who have vaccinated and thereby accomplished primary vaccination series (currently one or two doses of COVID-19 vaccine depending on the product) and with time, the immunity and clinical protection has fallen below a rate supposed to be appropriate in that population.
- The objective of a booster dose is to reinstate vaccine success after a certain time elapses
- On January 3, 2022, authorization of Pfizer-BioNTech COVID-19 vaccine was extended to include population aged 12–15 years in addition for all persons aged ≥12 years. The time interval between second dose and booster dose was reduced to ≥5 months
- COVID-19 boosters strengthen the protection against Omicron in addition to other SARS-CoV-2 variants. Monitoring of adverse effects of booster doses in age group of 12-17 years showed that reactions after vaccination with Pfizer-BioNTech booster dose were usually mild to moderate and temporary and the incidence of serious adverse events was rare.

https://www.fda.gov/media/150386/download
https://www.cdc.gov/media/releases/2022/s0105-Booster-Shot.html
Budesonide in Covid-19

- Budesonide an inhalational steroid has been widely used for asthma and chronic obstructive pulmonary disease (COPD).
- Inhaled budesonide has reduced the time for recovery in patients with high risk COVID-19.
- The evidence for this was obtained from the trial for community based treatments for COVID 19 called “PRINCIPLE”. Here, budesonide was given by inhalation route at the dose of 800 mcg every 12th hourly for 14 days. They were followed-up after 28 days.
- Patients treated with inhaled budesonide recovered faster and had better wellbeing. This is a significant landmark for this pandemic.

https:// ipc.gov.in/images/PvPI_Newsletter_issue_37.pdf. Newsletter Pharmacovigilance program of India (PvPI) VOL 11 I Issue 320 l 2021. ISSN:2320-7760

Drug Safety Alerts (PvPI)

Listed below are Suspected and Unexpected Serious Adverse Reactions (SUSARs) from the Pharmacovigilance Program of India (PvPI) database  (Dec-2021 to March 2022)

<table>
<thead>
<tr>
<th>Suspected Drug</th>
<th>Indication</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>Antiviral drug. Also used in COVID-19</td>
<td>Sinus bradycardia</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Hypertension</td>
<td>Nipple pain and supress lactation</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Thyroid cancer</td>
<td>Colitis</td>
</tr>
</tbody>
</table>

US-FDA Drug Alerts

The following drug safety alerts were issued by the U.S. Food and Drug Administration (FDA) from Jan-Mar 2022.

1. There might be a risk of death with the drug **umbralisib** which is used for lymphomas. The physicians need to weigh the risk and benefits of this drug before prescribing. FDA is continuing to analyse the results obtained from UNITY trial.

2. FDA has warned regarding dental problems secondary to mouth dissolving **buprenorphine**. These include tooth decay and cavities leading to loss of teeth as well as oral infections.

## New Drug Approvals

The following drugs were approved by the US-FDA (Dec-March, 2022):

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Active Ingredient</th>
<th>Used in treatment of</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opdualag</td>
<td>nivolumab and relatlimab-rmbw</td>
<td>Unresectable or metastatic melanoma</td>
<td>18/03/2022</td>
</tr>
<tr>
<td>Ztalmy</td>
<td>ganaxolone</td>
<td>Seizures in cyclin-dependent kinase-deficiency disorder</td>
<td>18/03/2022</td>
</tr>
<tr>
<td>Vonjo</td>
<td>pacritinib</td>
<td>Myelofibrosis in adults</td>
<td>28/02/2022</td>
</tr>
<tr>
<td>Pyrukynd</td>
<td>mitapivat</td>
<td>Hemolytic anemia in pyruvate kinase deficiency</td>
<td>17/02/2022</td>
</tr>
<tr>
<td>Enjaymo</td>
<td>sutimlimab-jome</td>
<td>Reduces requirement of red blood cell transfusion in hemolysis caused due to cold agglutinin disease</td>
<td>4/02/2022</td>
</tr>
<tr>
<td>Vabysmo</td>
<td>faricimab-svoa</td>
<td>Age related macular degeneration and diabetes induced macular edema</td>
<td>28/01/2022</td>
</tr>
<tr>
<td>Kimmtrak</td>
<td>tebentafusp-tebn</td>
<td>Unresectable or metastatic uveal melanoma</td>
<td>2501/2022</td>
</tr>
<tr>
<td>Cibinqo</td>
<td>abrocitinib</td>
<td>Refractory, moderate-to-severe atopic dermatitis</td>
<td>14/01/2022</td>
</tr>
<tr>
<td>Quviviq</td>
<td>daridorexant</td>
<td>Insomnia</td>
<td>7/01/2022</td>
</tr>
<tr>
<td>Adbry</td>
<td>tralokinumab-lдрm</td>
<td>Moderate-to-severe atopic dermatitis</td>
<td>27/12/2021</td>
</tr>
<tr>
<td>Leqvio</td>
<td>inclisiran</td>
<td>Add on therapy for familial hypercholesterolemia or clinical atherosclerotic cardiovascular</td>
<td>22/12/2021</td>
</tr>
<tr>
<td>Vyvgart</td>
<td>efgartigimod alfa-fcab</td>
<td>Generalized myasthenia gravis</td>
<td>17/12/2021</td>
</tr>
<tr>
<td>Tezspire</td>
<td>tezepelumab-ekko</td>
<td>Add-on maintenance therapy for severe asthma</td>
<td>17/12/2021</td>
</tr>
</tbody>
</table>

**Semaglutide**

**GLP** $\rightarrow$ **GLP 1**

**Stimulates insulin secretion**

**Suppresses glucagon secretion**

**Route of administration:** Oral and subcutaneous

**Use:** Type II diabetes mellitus and to prevent development of cardiovascular disease in diabetics. It is also approved for chronic weight management in adults with either high blood pressure, type 2 DM, or high cholesterol in addition to adjunct measures like reduced calorie intake and increased physical activity.

**Adverse effects:**

i. Hypoglycaemia appears to be low; however, the risk is more when combined with oral hypoglycaemics and/or insulin.

ii. Injection site reactions with subcutaneous doses

iii. Gastrointestinal disturbances

iv. Pancreatitis and pancreatic cancer- have been reported in a few preclinical studies

v. Decreased gallbladder motility leading to bile stones

**Disulfiram in Retinal Degeneration**

**Disulfiram** in experimental studies improved sight in mice with retinal degeneration by inhibiting the enzymes involved in the production of retinoic acid. It may revive sight in patients with retinitis pigmentosa and other retinal degenerative disorders. Clinical trials in patients with retinitis pigmentosa are awaited.

Ref: Retinoic acid inhibitors mitigate vision loss in a mouse model of retinal degeneration” 18 March 2022, Science Advances.DOI: 10.1126/sciadv.abm4643

“Predicting the future isn’t magic, it’s artificial intelligence” - Dave Waters
Hans-Jürgen Hess has an illustrious record to his credit in the field of drug discovery and development. After being conferred with Ph.D. in organic chemistry in 1957, Hans Hess joined as a Research Chemist in 1959 in Pfizer’s Medical Research Laboratories in Groton.

In 1963, he discovered an antihypertensive agent, prazosin. It is a selective α1-adrenergic blocker and does not have an unfavourable effect on lipid profile like other antihypertensives. In 1988, prazosin was ranked third in the global market of antihypertensives. The drug is also effective against BPH (benign prostatic hyperplasia). The structural analogs of Prazosin namely terazosin, alfuzosin were later developed and endorsed for BPH. In the field of adrenergic receptor research, prazosin was considered as laboratory standard. Hans Hess, in 1991, was honoured with Pharmaceutical Manufacturers Association (PMA) Discovery Award for this novel discovery which is till date being used in various indications.

The non-FDA uses of prazosin include other conditions like benign prostatic hypertrophy (BPH), nightmares associated with post-traumatic stress disorder, pheochromocytoma, Raynaud phenomenon. Lately, in scorpion envenomation, prazosin has shown to reduce mortality when given in combination with standard therapy.