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Patient compliance with a prescribed drug regimen has been an important issue in clinical pharmacology, but measurement of compliance has presented challenges. Compliance has been estimated by counting returned, unused medication; by interviewing patients; or by having patients' complete diaries and questionnaires. These methods are strongly biased toward overestimation of compliance due to social pressure for the patient to seem compliant to the physician. Various methods of electronic medication event monitoring and chemical markers have been used to assess drug usage in clinical trials, although these chemical markers verify drug ingestion but give no information about the time of drug ingestion. In contrast, electronic monitoring devices provide detailed date and time records of opening the medication container, but they cannot prove that medication was ingested. Consequently, the combination of these two methods, electronic monitoring in combination with chemical markers, is currently regarded as the "gold standard" for compliance measurement in clinical trials.

INTRODUCTION

Is this drug safe ? Will it cure the disease ? What are its side effects ? Will it cause damage in the long term? What is the apt dosage for the drug? These are the questions that arise before a doctor, prescribe any drug. These are to be duly answered by any researcher to get the drug approved. Every new drug needs to go through the critical phase of clinical trials before it is launched in the market. Regulatory bodies such as Food and Drugs Administration (FDA) in the USA are responsible for approving whether a drug can proceed to clinical trials and whether it should be allowed on the market. The regulatory body has to evaluate the scientific and clinical data to ensure that the drug can be produced with consistently high purity, that it has the clinical effect claimed and that it does not have unaccepted side effects. It must also approve the labeling of the drug and directions for its use. In general, the regulatory body is interested in all the aspects of a drug once; it has been identified as a potential useful medicine.

Clinical trial is a research tool that validates a drug. Tactful handling of this phase of research, standardization of a clinical study by good patient monitoring practices, makes a drug successful and more importantly-safe. The successful conduct of a clinical trial depends upon the efficiency of the study design-The Protocol.

STRINGENT PROTOCOLS AND TRIAL PROCESS

The clinical trial protocol is a crucial document for the successful conduct of a clinical trial and as such, requires skill in design and writing. The key elements of protocol include the rationale for study, the study design, primary and secondary end points, inclusion or exclusion criteria, study procedures, methodology, safety testing, statistical power and study analysis, as well as safety reporting and logistical or administrative requirements. There are certain norms that researchers have to follow and tests that have to be done before including volunteers for a clinical study. Patients who take part in clinical trials must fulfill all inclusion criteria as per the trial protocol. Some of the inclusion criteria are age, sex, BMI, the type and stage of the disease. In addition, pathological investigation should be done on the patient like hematological tests, serology, biochemistry, urine analysis and tests for abusive drugs. A good protocol is highly focused and does not try to answer too many questions at once. Good design of a trial gives focus to a trial and guides all the processes.

The subjects or trial population who are recruited depend on the stage of a clinical trial. Like Phase I trials, pharmacokinetic studies, bioavailability and bio-equivalence studies are done which are performed on healthy human volunteers. Whereas, trials from Phase II to Phase IV are done on patients, where efficacy of the drug on the disease is tested.

- In Phase I clinical trials, researchers test a new drug or treatment for the first time in a small number of people (20-80), usually normal, healthy volunteers to evaluate its safety, to determine a safe dosage range and identify side effects.
- In Phase II clinical trials, the drug or treatment is administered to a larger group of people (100-300) to further assess its safety and effectiveness.
- In Phase III clinical trials, the drug or treatment is administered to large groups of people (1,000-3,000) to further determine effectiveness, monitor side-effects, compare it to commonly used treatments and collect information that will allow safe use of the drug or treatment.
- The Phase IV clinical trials are performed after the

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drug treatment has been authorized for medical prescription and has been marketed. These studies continue testing the drug or treatment to collect information on the effect in various populations and side effects associated to long term use. Patients are randomly assigned to the group receiving the new treatment (treatment group) or to the standard group (control group) to ensure the trials impartiality. Post approval studies further characterize the drug. These studies are intended to document the drugs clinical benefit. If the drug shows no clinical benefit the sponsor is required to voluntarily withdraw the drug from the market.

The recruited subjects are not allowed to participate in any other clinical trial for a period of three months.

PATIENT RECRUITMENT AND EDUCATION

Like the right soldiers make a strong army, right patients determine the success of a clinical trial. Moreover testing on humans is a sensitive and a difficult issue as it involves many legal and ethical issues. Even though a drug is passed to the human stage only after it successfully completes in-vitro testing and animal testing, side-effects of a new drug are always unknown, making patient recruitment and monitoring a very complex activity. Patient or volunteers or trial populations are the backbone of any clinical study and make a very valuable contribution to the testing of the efficacy of a drug. Patient selection for a therapeutic segment depends upon the design of the study and complexity of the issues to be answered. [1, 2]

Patient recruitment consumes almost one third of the time and drug development budget. It is also the most critical bottleneck in clinical research. Of all clinical trials conducted globally, more than 80 percent are delayed due to slow patient recruitment (the funnel effect). Yet another important aspect of the patient recruitment is educating the patient about the intricacies of the study. Patient education will help to ensure compliance on the part of the patient, like giving them complete details like - what is the drug that they are taking, its strength, the use of the drug and the adverse events.

FDA information sheets have laid down guidance on advertisement for recruitment of patients to be followed by IRBs and Clinical Investigators…

"… The procedure for recruiting subjects is not coercive and does not state or imply a certainty of favorable outcome or other benefit beyond what is outlined in the consent document and protocol."

No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purpose under investigation…"

"Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" implies that all study subjects will be receiving newly marketed products of proven worth."

"Advertisements should not promise free medical treatment, when the intent is only to say (the) subject will not be charged for taking part in the investigation. Advertisements may state that subjects will be paid (recruitment incentive, not a benefit of research), but not emphasize the payment or amount paid".

"Any advertisement to recruit (research) subjects should be limited to the information the prospective subjects need to determine their eligibility and interest." [3]

SAFETY ISSUES

Good Clinical Practices (GCP) specifies strict guidelines that protect people, who choose to participate in clinical trials. All clinical trials must be approved and monitored by the Institutional Review Board (IRB) and the Ethics Committee (EC) to make sure that the risks are as low as possible and are worth any potential benefits. The IRB and EC reviews the trial protocol and ensures the scientific content of a clinical trial, its scientific importance, the cogency of the hypothesis, appropriateness of the experiment plan, statistical analysis, adequacy of participants and feasibility with regard to the completion of the trial within a reasonable time-frame.

EC is an independent committee composed of physicians, pharmacists, nurses, experts inbioethics, legal affairs, patients' rights and other experts. EC ensures the ethical content of the trial and safeguards the rights and of all trial participants. According to GCP, patients must be fully aware that they have rights both before they give consent to participate in a clinical research study and during treatment.

All clinical investigations, including physiologic, toxicity, and dose finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III), involving greater than minimal risk to participants are, at a minimum, required to develop a data and safety monitoring plan to assure the safety and welfare of the research subjects.

A Data Safety Monitoring Committee (DSMB) is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the study is unlikely to be concluded successfully. Monitoring should be commensurate with size and complexity of the study. At a

minimum, a DSMB should be developed and included as part of the electronic IRB application. The plan should contain the following information:

- An explanation of the plan to monitor progress and safety;
- Specific predetermined safety reviews to be conducted by an assigned board, committee or individual monitor;
- Depending on the complexity of the research, the plan may include assessments of data quality, timeliness, participant recruitment, accrual and retention;
- A description of the plan to assure compliance with reporting of adverse events and/or unanticipated problems involving risk to participants or others;
- A description of the plan to assure data accuracy and protocol compliance.[4-11]

DESIGNING AND MONITORING PATIENT COMPLIANCE

"Drugs don't work in patients who don't take them." This well known quotation of former US surgeons General C. Everett Koop implies a basic fact of medical therapy and the consequences of non-compliance. The consequences of non-compliance to therapy in clinical trials are injurious to correct conclusions.

WHAT IS COMPLIANCE

Drug regimen compliance is defined as: the degree of correspondence between actual dosing history and the prescribed regimen. This means that the administration/ intake of a correct dose of the drug must take place at a defined time of intake, and the patient will continue in doing so for the whole period of treatment.[12]

Perhaps the most critical point for measuring patient compliance is during the clinical research trials used to determine the efficacy of new pharmaceuticals. On the basis of the results of such trials, new medications are either licensed for general medical use or abandoned. Clinical trials data also determine the recommended dosing strategies for specific clinical indications. Consequently, inaccurate data during clinical trials can result in decisions that will affect everyone who uses the drug during its lifetime–tens of millions of patients in the case of widely used drugs. It can also result in a potentially therapeutic drug being unnecessarily abandoned.

Best practice guidelines in clinical pharmacotherapy are designed to maximize the therapeutic effect of medications while minimizing side effects and cost. The dose, dosing interval, and duration of pharmacotherapy are based on the best estimate of the time during which a therapeutic plasma level will achieve the desired therapeutic effect. New medications are tested clinically on patients having the disease of interest, and the outcome contributes significantly to the best practice guidelines. Patient compliance with the dosing regimen during clinical trials is critical to establishing accurate dosing guidelines.

In a clinical trial, poorly compliant patients may require an average of 10 days to cure; perfectly compliant patients only five days. However, due to individual differences, some poorly compliant patients may need 12 days of therapy and some perfectly compliant patients may require only three days. The ensuing best practice guidelines must ensure that all patients being treated will be cured. Thus, physicians prescribing the drug for the rest of its life will prescribe it for 10 days for everyone although for compliant patients only five days are necessary. If the physician knew a patient was perfectly compliant, he or she could prescribe a five-day course of the antibiotic with confidence. Conversely, if a non compliant patient did not respond to the antibiotic the prescribing physician might educate the patient and continue the same antibiotic rather than assuming the drug is resistant and changing to another antibiotic. In both scenarios, knowledge of the patient's compliance would have positive implications for health care at the macro level.

Patient non-compliance can affect the health care system via clinical trials at another level. Lack of compliance during the trial of a new drug could bias the results, causing an effective drug to be abandoned or requiring, unnecessarily, more extensive (and expensive) testing to demonstrate a drug's effectiveness **Table-1**. Researchers and clinicians have used numerous methods in their attempts to adequately assess patient compliance (adherence) with medication regimens and to identify noncompliant patients. Large variations have been reported in the extent of noncompliance in individual patients and large populations. In addition, non-adherence has often been poorly defined. Direct measures of adherence include drug assays of blood or urine, use of drug markers with the target medication, and direct observation of the patient receiving the medication. Indirect measures of adherence imply that the patient has used the medication; these measures include various forms of self-reporting by the patient, medication measurement (pill count), use of electronic monitoring devices, and review of prescription records and claims. [13-19]

"SMART" MONITORING BY ELECTRONIC DEVICES

Patient diary is one tool often used. The patient has to state time of administration immediately as it occurs. However, data from a diary is at least questionable, as a

Table - 1

Reason for Non Compliance	Relevance for Clinical Trials/Possible Solutions
PATIENT-RELATED	
Misunderstanding of prescribing instructions	• Are clinical trial labels designed to meet regulatory requirements, or to aid the patients? • Has the sponsor trained the investigator/pharmacist in correct use of medication? • Has this been relayed to the patient during visits?
Denial/Embarrassment	• Patients may feel that a large, indiscreet pack advertises their ailment to others. • Drug may be removed in advance and transferred to other containers, affecting compliance.
Forgetfulness	• In calendar-type blister packs and cards, it is more obvious to the patient whether or not they have taken their medication at the correct time. • Is there any kind of follow up to remind the patient to take their medication as directed? • Smart packaging could help.
No faith in drug's effectiveness	• This may be especially true in a clinical trial, but may be addressed through investigator counseling and other forms of patient education. • Not specific to clinical trials.
Reduction, fluctuation or disappearance of symptoms Apathy	• Patient education programs are becoming common place in encouraging patients to participate in clinical trials and help alleviate this.
PHYSICAL DIFFICULTIES Swallowing tablets or capsules	• Blinding products by over-encapsulation can result in unit doses that may effect compliance.
PACKAGING DIFFICULTIES Opening packages	• Small packs/medication unit can be difficult for elderly patients to manipulate. • Some blister designs can make it more difficult to remove medication. • Large packs are inconvenient. Patients may remove drug and transferred to more convenient packaging, effecting compliance. • Child resistant packaging are generally more difficult for patients to open.

paper in BMJ showed a very high discrepancy between patient-reported events (as intake) and the actual access to the diary, which was monitored by means of a timer hidden in a cover for a paper diary. The term "car park compliance" and "white coat compliance" (poor or partial compliers improving their compliance around the time of scheduled following visits) are important notions, which must be taken seriously, because investigators might reach incorrect conclusion with respect to effects caused by non-compliance or by the test drug itself. Also, "white coat compliance" pattern makes therapeutic drug monitoring a potential unreliable tool for long-term drug exposure. The most widely used techniques for monitoring compliance with medication are pill counts and medication diaries. These are used in most clinical pharmaceutical trials, and rarely in clinical settings. The former technique involves counting the number of pills returned to the study monitor at the end of an interval and checking to see if this is congruent with compliance. In the latter, patients keep a diary of their medication-taking and may also record side effects, clinical response, and other events of interest. The data can then be used to assess compliance and, if desired, target education to non-compliant patients. Unfortunately, both have been demonstrated to be ineffective. Patients are prone to filling out diaries retrospectively just before meeting with the study monitor or "adjusting" their medication to compensate for missed doses. Neither pill counts nor medication diaries address the issue of patients not taking their medication on schedule. Yet, despite their limitations, these techniques remain the industry standard.

Until 1986 to 1987, the estimation of patient compliance with prescribed drug regimens in ambulatory care relied on methods that were biased either by their subjectivity or by the improvement in compliance that commonly occurs during the day or two prior to a scheduled examination, so called 'white-coat compliance'. In 1986 to 1987, 2 objective methods were developed: electronic monitoring and low-dose, slow-turnover chemical markers (digoxin or phenobarbital [phenobarbitone]) incorporated into dosage forms. While neither method is without limitations, both have enabled major advances in the understanding

of patients' compliance with dosage regimens and, thus, the spectrum of drug exposure in ambulatory care. The new methods have also triggered not only a revival of interest in patient compliance and its determinants, but also new statistical approaches to interpreting the clinical correlates of widely variable drug administration, and thus drug exposure, in drug trials. The marker methods prove dose ingestion during the 3 to 7 days prior to blood sampling, but do not reveal the timing of doses.[19-21]

The electronic monitoring methods, i.e. time and date-stamping micro circuitry incorporated into drug packages, provide a continuous record of timing of presumptive doses throughout periods of many months, but do not prove dose ingestion. The electronic record has been judged robust enough to detect certain types of investigator fraud, and to support modeling projections of the complete time course of the plasma drug concentration during a trial. Both marker and electronic methods show that the predominant errors are those of omission, i.e. delays or omissions of scheduled doses. Patient interviews, diaries, and counts of returned, untaken doses have been shown by both marker and electronic monitoring methods to consistently and substantially to overestimate compliance. Monitoring of plasma drug concentrations also overestimates compliance; because white-coat compliance is prevalent, and the pharmacokinetic turnover of most drugs is rapid enough that measured concentrations of drug in plasma reflect only drug administration during the period of white-coat compliance. Thus, compliance is a great deal poorer in clinical trials than has been revealed by the older methods. The long-standing underestimation of poor compliance in drug trials has many implications for the interpretation of drug trials, for optimal dose estimation, for the interpretation of failed drug therapy, and for accurate labeling of prescription drugs.

The introduction of radiofrequency identification device, RFID tags-enabled computer chip technology has introduced the possibility of monitoring that a patient has taken medication, and when the medication was taken. It is evident that pharmaceutical products-even within identical indication-differ widely in the degree of compliance needed in their dosing schedules.[22-24]

Med-ic ECM (electronic compliance monitor)

Focusing on the financial and human costs associated with medication non-compliance, Information Mediary Corporation has developed the Med-ic™ ECM™ Package, an electronic device that provides precise inventory monitoring in clinical settings for blister–packaged medication. The use of electronic compliance packaging continues to grow, with two recently launched products joining the fray. MeadWestvaco Healthcare Packaging (Mebane, NC) has begun initial testing of Cerepak, an electronic update Dosepak package. Information Mediary Corp. (IMC; Ottawa, ON, Canada), meanwhile, is currently testing the Med-ic ECM blister package. Cerepak employs smart technology to measure and improve patient compliance. It reminds patients when to take medication, records when they do, and reports that data back to their doctor or pharmacist. The package's built-in 'brain' also provides real-time compliance measurement that can expedite drug development through clinical trials, enhance patient persistence, and improve the bottom line. The technology allows the removal of each pill from a blister package. When a pill is removed, the package emits a slight beeping noise, recording the time and date of removal of medication. It also records which pill has been taken. In addition, a patient questionnaire is integrated into the package, featuring a log for patient side effects and time to onset. The questionnaire also measures pain and nausea. IMC's Med-ic is also currently being tested in clinical settings. The package uses an electronic device that is integrated into a blister package. It tracks medication usage without active patient input and contains an RFID smart tag that records the time at which the tablet or capsule is expelled, logging the patient's medication use. Following completion of a clinical trial, the patient can return the blister package to a clinician, who uses the RFID scanner to download the information into a database. The data are downloaded through a 13.56-MHz RF wireless reader to a researcher's computer.

The Med-ic ECM is designed to streamline clinical data collection. It also integrates IMC's CertiScan peripheral hardware and software with IT and packaging engineering support. The Med-ic™ ECM™ Package can be tailored for specific clinical requirements including monitoring temperature, vibration, humidity, light, radiation or shock to which the blister package has been exposed and recording the time of the exposure. Visual and auditory reminders, including LCDs, can also be integrated with the device as required. The Med-ic™ ECM™ Package uses a proprietary, disposable, nontoxic power cell and is environmentallysafe.

eCAP, a smart RFID closure for medication bottles and vials. It consists of the Med-ic RFID smart tag embedded in a Remind Cap bottle closure. Similar to the other packages, it reminds the patient when the next dose is due and records the time the patient opens the bottle to remove the tablet or capsule, logging compliance at that moment.

The recorded data are then retrieved with IMC's CertiScan reader for a physician or pharmacist to review.[25, 26]

Medication Event Monitoring System (MEMS®)

The most successful microelectronic device primarily used in clinical trials is Aardex's MEMS device, a pill bottle with a cap that transmits data to a server, and reminds the patient to take his medicine.

The Medication Event Monitoring System (MEMS®) measures and analyses the compliance of patients to prescribed drug regimens:

- By collecting real time data on the patients monitor
- By transferring the data from the monitor to a personal computer by means of a communicator
- By storing the data in database
- By displaying and printing reports of the results (tables and plots).

THE PRINCIPAL COMPONENTS OF THE MEMS® ARE

- MEMS® monitors that collect real time data and store the data in a non-volatile internal storage unit
- A communicator that transfers the data from the monitor to a personal computer
- A computer program such as PowerView® that stores the data in a database calculates the results and displays or prints reports of these results.

TECHNICAL DETAILS

The MEMS® 6 monitors, is a new generation electronic monitor and replaced the MEMS®V monitors. The main difference between MEMS®V and MEMS® 6 is the way the data is transferred between the monitor and the communicator. MEMS®V uses a capacitive coupling, and MEMS® 6 uses an inductive transmission.

The MEMS® IV is a medication compliance bottle monitor containing microelectronics that records the time and the date the bottle is opened. Its electronic memory can also store information about the patient and drug. The monitor provides a means of objectively measuring a patient's compliance with prescription drug regimens.[27]

Intelligent Drug Administration System (IDAS)

There are other devices primarily designed to regulate dosing that could be used to ensure patient's compliance. Some of these systems are disposable card-boxes, which can be up-loaded through a computer at the investigator site. Other strategies include reusable intelligent drug administration systems that accommodate blister strips. B&O Medicom has developed two such devices. Internally, they are referred as IDAS I and IDAS II respectively. The IDAS I is an electronic device with a multicolored diode display that serves as a reminder and even as a compliance indicator. The device registers every time the blister strip is taken out, signifying that a tablet/capsule has been swallowed. IDAS II device works with blister strips that have conductive lines printed on thin foil covering the plastic wells containing an active drug as tablet or capsule. The blister strips are held in a monitor that is equipped with contact points for the conductive lines. A microprocessor sends electric current through the conductive lines at regular intervals and, when the patient takes a tablet/capsule from the pack, the foil and conductive lines are broken. This is registered in the microprocessor as a tablet has been taken. The information is stored in the blister monitor's memory. The dosing data are then loaded onto a PC or a server, enabling physicians and investigators to perform detailed analysis of each and every patient's dosing history, therapeutic coverage, and drug holiday and so on. IDAS II also has audible and visual indicators to remind the patient to take their medication. Its LCD screen shows the time since last dose, actual time and a battery indicator.[12]

e-pill electronic "pill" dispenser (Medtime XL automatic medication dispenser/pill organizer/pill box, Med-Time XL) and reminder system helps ensure that medications and vitamins are taken properly (pill identification) and on time.

Med-Time XL is a device for dispensing medicine, reminding the user when medicine shall be taken, and making the correct dose available.[28]

DISCUSSION

Compliance measures should be assessed on the basis of their validity (sensitivity and specificity or statistical correlation) and the reference standard used. Many early studies used pill counts as a reference standard, but electronic monitoring devices such as the Medication Event Monitoring System have replaced pill counts as the reference standard. The choice of a method for measuring adherence to a medication regimen should be based on the usefulness and reliability of the method in light of the researcher's or clinician's goals. Specific methods may be more applicable to certain situations, depending on the type of adherence being assessed, the precision required, and the intended application of the results.

A parameter called 'Forgiveness' defines the margin for errors in dosing timing that can be allowed without preventing the patient from gaining benefits from the drug. The claim 'Forgiveness' derives basically from an un-changeable pharmacokinetic feature such as long half-life in plasma, tissues etc.

By measuring plasma concentration of the test drug one will get compliance data on the actual day of sampling and not between visits. However it must be emphasized that well controlled and close monitoring of compliance is of major importance in order to correlate plasma concentrations (pharmacokinetic) with pharmacological effect, i.e. pharmacodynamics and adverse effects in Phase II trials. None of the traditional ways of monitoring compliance are instant measures or allow for intervention to help the patients get their drug regimen back on track and in doing so demonstrate the full potential of the test drug.

CONCLUSION

Hippocrates, the father of medicine, already realized that "the physician must not only prepared to do what is right himself, but also make the patient…cooperate". Medical compliance-commonly defined as the extent to which a patient conforms to medical advice about lifestyle and dietary changes as well as taking medications, as prescribed-remains a challenge more than twenty centuries after Hippocrates.

With advanced research techniques, medical science is progressing at a frenetic pace. Several diseases are being diagnosed in the early stages improving the quality of human life. Our huge population has attracted the attention of the pharmaceutical industry from the developed nations for conducting clinical research. Several contract research organizations are also gearing up to organize themselves in the field of human clinical trials. Hitherto, Phase II and Phase III clinical trials on new drugs were conducted only at selected medical college hospitals; where there is ready availability of 'volunteers' suffer from various disease.

In India, Phase IV clinical trials are currently undertaken in most public and private clinics or hospitals. It needs to be emphasized that in most cases, volunteers are not paid any fees for being a part of the trial study. Volunteers are recruited with a cursory explanation of the trial procedure and their consent is obtained. Conversely, a volunteer without commitment would not stick to his follow-up schedule, which is detrimental to clinical research. Also, every 'drop-out' case is an avoidable expense for the drug manufacturer and the investigating team. If adequate safeguards are incorporated in the protocol, the investigator can clearly explain the trial process to his volunteers. Consequently, the investigating physician will be in a better position to enroll the requisite number of cases and maintain accurate data of the patient's progress or the lack of it. The paid volunteer will have sufficient incentive for follow-up visits providing the investigator with valuable inputs into the drug's efficacy. Failure to introduce safeguards into clinical trials would result in the mushrooming of fly-by-night 'trial operators', who will not only harm the interest of genuine patients but also churn out unreliable clinical data.

Application of pervasive computing technologies can significantly help patients manage their diseases and hence improve patient adherence (patient compliance) to medical treatments. The scenario envisioned is one in which smart medication-medication package augmented with pervasive computing technologies- informs the patient about the effectiveness and side effects of the treatment, sends reminders to take medication, informs relatives of elderly patients about their adherence to treatment, detects dangerous combinations between different types of medication and alerts users about recalls or expired medication.

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