More than 50 Jefferson County residents attended a meeting on July 7, 1953 at the Crystal City Hotel to discuss the need for a local community hospital. They formed an association and pledged $800 toward a study on the feasibility of the project. In those days, the Pittsburgh Plate Glass company dominated the local economy, and although the PPG plant had its own "hospital" that was available in emergencies, it simply did not meet the needs of the growing population. Doctors had to send serious cases to St. Louis, a drive of at least 45 minutes on a winding two lane road, since Interstate 55 had not yet been built. Ambulance services were provided by the local funeral homes, so it was likely that the trip to St. Louis would be made in a hearse. The need became clear, and local supporters from all walks of life stepped forward to make the hospital a reality.

Sam Linder, Crystal City druggist and chairman of the Festus, Crystal City Chamber of Commerce hospital committee, was elected president of the hospital association. Mr. Linder stated at the public meeting that an anonymous donor had offered a 15 acre site near the Twin Cities and De Soto, two of the largest centers of population in the county, for the proposed hospital. A representative from the bureau of public health engineering spoke on the Hill-Burton bill, a federal law which allows the U.S. government to pay 50 percent of the construction costs of a non-profit hospital. An application for federal aid and plans for a 50 bed facility were submitted to Jefferson City the following morning.
Amos Govero, a local business and civic leader of Festus, began appealing to local businesses and organizations to garner support for the project. He eventually helped to secure about $1 million in funding to establish JMH. The first board of directors, with Mr. Govero as chairman, met in August 1953.

The board was able to secure a federal grant for $350,000, approximately half of the projected cost of construction, provided that the community could raise the other half. Various methods of fundraising were used, including selling "subscriptions" for $10. These were essentially a non-voting, non-dividend paying "share" in the hospital. Rooms and spaces in the hospital were available for sale as memorial units. Employees from some of the local businesses made donations by having an ongoing deduction from their paycheck. Local businesses donated funds, as well as private donors. Clubs, societies, and even school children contributed to the effort. When the deadline arrived on March 12, 1954, the necessary funds were collected and construction began in 1955. The total cost of the completed project amounted to more than a million dollars. Additional funds were needed to equip the hospital, and to pay for improvements, so the fundraising efforts continued, and a loan for $100,000 was taken out with the Citizen's Bank of Festus.
While the hospital was under construction in the early days of 1957, their "command headquarters" was located in the upstairs of the Liberty Creamery, located in Crystal City, where Mrs. Betty Franke conferred with the Hospital Administrator, True Taylor. They worked to purchase equipment, food, china, flatware and hired hospital staff.

Mrs. Carol Carron became the first employee hired for the dietary department and her husband was hired as a male orderly. Mary Brown was put in charge of setting up the central supply. Some of the early duties of hospital staff were making alcohol balls, mixing infant formula, cutting gauze into pads, cleaning and powdering rubber gloves, and cleaning, sharpening and sterilizing syringe needles.

The hospital officially opened to the public on May 15, 1957, with thirteen employees and three physicians on staff. The first patient - Clara Smith of Crystal City came to the emergency room on opening day. Less than a day later, the first baby, Connie Nadine Woodland, daughter of Mr. & Mrs. David Woodland was born with Dr. Frank Kozal as the attending physician. 669 babies were born here in the first year.

Bea Smetzer was hired as an aide in the nursery. Ethel Akins became one of two registered nurses when she joined the staff one month after the hospital's opening and Georgia Smith joined the housekeeping staff.

A Volunteer Auxiliary, also known as the "Pink Ladies," was formed in 1958. They raised money for the hospital by operating the gift shop, vending machines, and a traveling gift/snack cart. They also sponsored blood drives, and escorted patients throughout the facility. One of their fundraising projects was a cookbook of recipe "secrets" authored by the ladies.
Harry Davis was the first hospital administrator, followed by True Taylor. Amos Govero, the first board chairman passed away in 1961, and Edward T. Eversole took his place.

The hospital received national attention when they were featured as "Hospital of the Month" in a 1959 issue of Modern Hospital magazine.

By 1963, the original debt had been paid off, and the hospital was looking to expand again. The hospital had been designed so that a second floor could be added. With that in mind, another federal grant, and another fundraising drive to pay for the project began. Construction for the second floor expansion, making a total of 98 beds, was completed in 1965.

The first patient in the new wing was Thomas Alexander, as shown in this newspaper photo.
In 1974, construction began for yet another expansion which included more than 100 patient beds, eight private rooms, six new operating rooms and a new location for the emergency room entrance. A News Democrat article stated that "the new wing of Jefferson Memorial hospital will be named in honor of Ed Eversole, called the Guiding Force behind the growth of the hospital since becoming board chairman in 1961. Dedication date is Sunday, September 18, 1977."

A new pediatric wing, an emergency room, and physical therapy and outpatient surgery facilities were added in the 1980's followed by dialysis services, skilled nursing facilities, surgical intensive care, a cancer center, outpatient X-ray and imaging, and many other services during the 1990's and into the 2000's.
The number of physicians and hospital staff grew greatly during this period of time. By 1992 the hospital employed 1000 people, and by 1996 that number had grown to 1500. Jefferson Memorial had become the largest employer in Jefferson County.

The hospital's name was changed to Jefferson Regional Medical Center on January 1, 2009. The Jefferson Memorial Hospital Association, established as a pro forma decree benevolent corporation in 1953 was dissolved, and a new non-profit, Jefferson Health Systems, was created. The new nonprofit was governed by the same board of directors who managed Jefferson Memorial.
In April 2010, a new short stay Surgical Hospital, Missouri’s first, opened across the street from the main Jefferson Regional Medical Center facility. It featured four operating rooms, two endoscopy rooms and fifteen private patient suites.

Mercy healthcare system took over operations of the hospital in 2013. The official transfer took place on January 31. The hospital at that time had 251 beds. They are currently building a new patient tower, changing the front entrance, and relocating services within the building to make it more patient friendly.